PEDIATRIC ADVISORY COMMITTEE MEETING

FOOD AND DRUG ADMINISTRATION

Thursday, September 22, 2011

1:59 p.m.

Hilton Gaithersburg Hotel

620 Perry Parkway

Gaithersburg, Maryland 20877

PARTICIPANTS

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DR. JOSE ROMERO
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DR. FRANK BALIS
MS. MARILYN EICHNER
DR. CARL D'ANGIO
MS. AMY CELENTO
DR. ALLEN VAIDA
DR. ANN MCMAHON
DR. DIANNE MURPHY
DR. LISA MATHIS
DR. JUDITH COPE
DR. KEITH KOCIS
DR. KATHLEEN MOTIL

DR. MICHAEL WHITE
DR. JEFFREY BRINKER
DR. CYNTHIA KORNEGAY
DR. TOBIAS GERHARD
DR. THOMAS LAUGHREN
DR. AMY TAYLOR
DR. LAURA GOVERNALE
DR. MITCHELL MATHIS
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DR. THERESA FINN
DR. MELISSE BAYLOR
DR. PATRICIA ROHAN

P R O C E E D I N G S

DR. ROSENTHAL: All right. Well, my watch says 1:59 p.m. I'm not sure we've ever started a Pediatric Advisory Committee meeting early. But maybe we'll get started today and see how things go.

Thank you all for coming to the Pediatric Advisory Committee meeting. We have really a very full agenda, both today and tomorrow. And so, let's just get started.

Walt is going to read a statement, and then we'll go around the table and introduce ourselves, and then we'll get right at it.

DR. ELLENBERG: Good afternoon. I'm Walt Ellenberg. I'm the designated federal official with the Office of Pediatric Therapeutics at FDA.

The following statement is with regards to conflict of interest in relation to the information that we'll be addressing at this meeting. I'd like to thank the members of the Pediatric Advisory Committee and the members of the public, as well as members of FDA, for putting in the time and effort to attend this meeting for these important discussions.

The following announcement addresses the issues of conflict of interest with regards to today's discussion of reports by the agency as mandated by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it's been determined that those individuals who will be participating in each topic do not have a conflict of interest for the following products: Fluarix, Afluria, Abilify, Akten, Famvir, Levaquin, Navstel, Retrovir, Topamax, Triesence, Videx EC, Ziagen, Zomig Nasal Spray, Kaletra.

And then, as mandated by the Food and Drug Administration Amendments Act, Title III, the Pediatric Medical Device and Safety Improvement Act of 2007, the committee will discuss the safety and profit-making waiver for the pediatric humanitarian device the Melody Transcatheter Pulmonary Valve and Ensemble Delivery System.

There will also be an update on a study that was jointly funded by the Agency for Healthcare Research

and Quality Act, better known as AHRQ, and the FDA on antipsychotic use and metabolic effects in children.

In general, the committee participants are aware of the need to exclude themselves from involvement in the discussion of the topics of their interest if their interest would be affected, and their exclusion would be noted for the record.

We note that Amy Celento will be participating as a consumer representative, and Ms. Marilyn Eichner will be participating as the patient-family representative.

The following experts are participating as temporary voting members: Dr. Frank Balis, Dr. Jeffrey Brinker, Dr. Michael White, Dr. Marcia Carney, Dr. Rick Chappell, Dr. Jose Romero, Dr. Jonathan Mink, Dr. Leon Dure, Dr. Keith Kocis, Dr. Allen Vaida, and Dr. Carl D'Angio.

There are several individuals who will be recused from the various aspects of the discussion at today's meeting -- one for today, several for tomorrow. Dr. Carl D'Angio will not participate in the discussions of Fluarix and Afluria. He will slide his chair back from the table. He will not participate in discussion, nor

will he vote on any of the issues.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment on.

We have one open public comment period, which is scheduled for tomorrow at 2:00 p.m.

Copies of the information presented at this meeting will be available online.

And I'd just like to remind everybody to turn on your microphones when you speak. Speak clearly and talk right into the microphone so we can hear you. The fans in this room are loud. So we noticed it may be difficult to hear everybody. So be cognizant of the fact that you need to speak up.

Also, for those in the room, the committee members and the public, please silence your cell phones.

And thank you very much. We'll begin the meeting.

DR. ROSENTHAL: All right. Just one thing I'd like to add to what Dr. Ellenberg has said. The discussions that we have, we need to have in the context of the meeting with the microphones on. Please

don't talk about the contents of the meeting outside. It's very important that we maintain a transparent and open system by adhering to that request.

So let's go around the table and just introduce ourselves.

Dr. McMahon, will you get us started?

DR. MCMAHON: Sorry. I'm Ann McMahon. I'm in the Office of Pediatric Therapeutics.

DR. MURPHY: Dianne Murphy, Office of Pediatric Therapeutics, FDA.

DR. LISA MATHIS: Lisa Mathis, Office of New Drugs, FDA.

DR. KOCIS: Keith Kocis. I'm a professor of anesthesia and pediatrics at the University of North Carolina in Chapel Hill, and I'm a pediatric cardiologist and critical care medicine physician.

DR. MOTIL: Kathleen Motil. I'm a pediatric gastroenterologist at Baylor College of Medicine and Texas Children's Hospital.

DR. WHITE: Michael White. I'm a pediatric cardiologist from the Ochsner Clinic Foundation in New Orleans.

DR. BRINKER: Jeff Brinker, professor of medicine and radiology, cardiologist for adults at Johns Hopkins University.

DR. ROSENTHAL: My name is Geoff Rosenthal. I'm a professor of pediatrics at the University of Maryland School of Medicine. I'm the chair of the Pediatric Advisory Committee, which is why I get to sit next to Dr. Ellenberg. And I'm a pediatric cardiologist.

DR. ELLENBERG: Again, I'm Dr. Ellenberg, designated federal official from the Food and Drug Administration.

DR. RAKOWSKY: Good afternoon. My name is Alex Rakowsky. I'm the IRB chair at Nationwide Children's Hospital in Columbus, Ohio. And I'm not sure why I'm sitting next to Walt.

(Laughter.)

DR. DURE: I'm Leon Dure, professor of pediatrics and neurology at the University of Alabama at Birmingham.

DR. TOWBIN: I'm Kenneth Towbin. I'm a child and adolescent psychiatrist in the intramural program at the National Institute of Mental Health.

DR. MINK: I'm John Mink. I'm a professor of neurology and pediatrics and a pediatric neurologist at the University of Rochester.

DR. WAGENER: Jeff Wagener, professor of pediatrics and pediatric pulmonary at the University of Colorado.

DR. ROMERO: I'm Jose Romero. I'm a professor of pediatrics and pediatric infectious diseases at the University of Arkansas for Medical Sciences and the Arkansas Children's Hospital.

DR. CHAPPELL: Rick Chappell, professor in the Department of Biostatistics and Medical Informatics at the University of Wisconsin Medical School.

DR. REED: Hi. I'm Michael Reed. I'm professor of pediatrics at Northeast Ohio Medical University, and I'm director of pediatric clinical pharmacology and toxicology at Akron Children's Hospital.

DR. BALIS: Frank Balis. I'm a pediatric oncologist at the Children's Hospital of Philadelphia.

MS. EICHNER: Marilyn Eichner, patient-family representative.

DR. D'ANGIO: Carl D'Angio. I'm associate

professor of pediatrics at the University of Rochester Medical Center, and I'm a neonatologist.

MS. CELENTO: Amy Celento, consumer representative.

DR. VAIDA: Allen Vaida. I'm a pharmacist from the Institute for Safe Medication Practices.

DR. ROSENTHAL: All right. Thank you all very much.

So our first speaker today is Dr. Judith Cope. Dr. Cope is a pediatric medical officer and epidemiologist with the Office of Pediatric Therapeutics, and that's in the Office of the Commissioner at the Food and Drug Administration.

She's been with the FDA for the past 8 years, working first with the Center for Devices and Radiological Health on pediatric device-related issues and then with the Office of Pediatric Therapeutics to focus on pediatric safety for FDA-regulated products.

Her clinical background is in adolescent medicine, general pediatrics, and in epidemiology. And Dr. Cope is going to talk to us about atypical antipsychotics and safety reporting to the Pediatric Advisory

Committee.

DR. COPE: Thank you.

Actually, just before I start, I just want to make -- publicly I want to thank the committee for all their work and expertise that they bring to these advisory committee meetings.

I also just want to lay out so you kind of see what's coming. We're going to be talking about antipsychotic studies. Then we'll have a safety reporting review that's mandated for Abilify, and then in the last 2 hours of the day, we're going to switch over to biologics.

But to start off with the atypical antipsychotics, I'm just going to give you a little background. There have been a couple Pediatric Advisory Committee meetings with products that have gone before, and I thought as a background, one of the slides from the earlier meeting was -- I thought laid it out, giving some points that are really key to remember.

One, schizophrenia and bipolar disorders are devastating diseases that often have an onset in childhood. Antipsychotic drugs are the cornerstone of

treatment and considered first line for pediatric patients. And the third bullet highlighting the atypical antipsychotics may have serious adverse reactions and need to be monitored, and there should be careful labeling. A comparative trial in children and adolescents would really further our understanding of all of this.

A little history then of the PAC meetings that have gone, thus, before. We've actually had three drugs that had mandated pediatric focused safety reviews to come before the committee, and many of you may have attended those meetings.

In November of '08, we had safety reviews, presentations for Zyprexa and Risperdal. And then, in December '09, we had Abilify.

I think it's important, too, we had that initial meeting and then when it came back in December '09, Abilify had its mandated review, but there were several other presentations for some of the ongoing issues and concerns that had been raised. There was actually a presentation of the use and the adverse events in the pediatric age group for five atypical antipsychotics.

There was a presentation by the National Institute of Child Health and Development that summarized a working group that had worked the year before about the area of research that was needed in this area. And then, actually, at that meeting, FDA reported very briefly that there was a jointly funded cohort study with AHRQ that was underway, and it was going to be evaluating the safety with the use of antipsychotics in the pediatric and older or adolescent age group.

And I just want to end with one more slide to just highlight that all the discussions, recommendations from the PAC, I just want to leave you with three points. One, the meetings and the PAC members raised concerns about the potential for metabolic effects that may be more common or severe in children and voted that the product labeling may not always adequately reflect the risks.

They also requested that FDA continue to focus on these safety issues with these products, and they discussed the need, the ongoing need for additional data for use in the pediatric population and really emphasized the need for databases to provide more

information.

So, with that, we're now going to have an FDA presenter talk about comparative studies, and then move on to a presentation of study by the principal investigator for the AHRQ-FDA study.

DR. MURPHY: I'm going to ask the FDA speakers to please introduce themselves with a single line about their background and training. Thank you.

DR. KORNEGAY: Good afternoon. My name is Cynthia Kornegay. I am an epidemiologist trained at the University of North Carolina in Chapel Hill, and I have been working in FDA's Office of Surveillance and Epidemiology since 2000.

In the next few minutes, I'm going to provide a brief overview of a collaboration between AHRQ and FDA to address antipsychotic safety in different populations. I will first provide some background on how the collaboration began, specifically for two of the studies focused on the comparative safety in children and adolescents. Dr. Tobias Gerhard will be discussing those studies in more detail shortly.

This collaboration is the result of combining

disparate efforts and interests at both FDA and AHRQ. FDA was specifically interested in the comparative safety of antipsychotics in institutionalized elderly patients with behavioral issues, a direct outgrowth of an earlier AHRQ investigation. FDA was independently investigating the association between antipsychotic use and prolactinoma, and there was a growing concern about the use of antipsychotics in children and adolescents.

At the time these investigations began, FDA had several questions of regulatory interest while the Agency for Healthcare Quality Research, or AHRQ, had a mandate to address safety issues and ongoing relationships with established investigators, as well as an interest in the comparative safety of antipsychotics. An FDA-AHRQ collaboration was the ideal solution to address several important safety questions at once.

The coordinating center for these studies was Rutgers University in Philadelphia. Individual studies were done by Vanderbilt University in Tennessee and Brigham and Women's Hospital in Boston, Massachusetts. The projects began in September in 2008 and are

scheduled to be completed September 30th of this year.

I was a steering committee representative for this collaboration. Additional Office of Surveillance and Epidemiology scientific, clinical, and administrative support was provided by Drs. David Graham, the associate director for science; J.R. Williams, an epidemiologist; and Kristin Phucas, the scientific administrator.

Clinical and scientific support from the Division of Psychiatry and the Office of New Drugs was provided by Laurie Duncan and Drs. Victor Crentsil and Robert Levin.

The results being discussed today are from two studies in child and young adult populations up to age 24. Some of the reasons for conducting this study were the increasing rates of antipsychotic use, polypharmacy patterns, and increased use in young children and very vulnerable populations.

In addition, there was little data available about the safety of these drugs in children and adolescents. These results will add to the sparse literature that currently exists.

The first study was a validation effort in the TennCare research database, based in Vanderbilt University. It provided researchers with the ability to validate the exposures, psychiatric comorbidities, and outcomes of medical records, and to develop accurate and valid computer-based algorithms to determine both exposures and outcomes of interest.

The study population was an incident user cohort of children who were prescribed atypical antipsychotics for selected psychiatric disorders, compared to children with the same diagnoses but who received treatments that did not include atypical antipsychotic therapy. Patients were age, gender, and propensity score matched for this analysis.

For the validation part, Vanderbilt University chose a random sample of 500 medical records for baseline covariate validation and an additional 205 records for the outcome validation. Based on the results of this study, the investigation was then replicated in the 45-state Medicaid extract dataset to enable characterization of and comparisons between individual drugs.

The size of the Medicaid extract dataset allowed for comparisons between individual drugs, which is not possible in the smaller Vanderbilt dataset. The results of these studies were recently presented at the International Society of Pharmacoepidemiology Annual Meetings in Chicago.

Dr. Tobias Gerhard from Rutgers University will now discuss the findings of these investigations.

Thank you.

DR. MURPHY: Dr. Gerhard, would you also please give the committee a few sentences about your background?

DR. GERHARD: Hello, everybody. Thank you, Cynthia, for the kind introduction.

My name is Tobias Gerhard. I'm an assistant professor at Rutgers University. That's in New Brunswick, not in Philadelphia.

My background is in pharmacy and pharmacoepidemiology. I have a pharmacy degree from Germany, and a degree -- a Ph.D. in pharmacoepidemiology from the University of Florida.

As Cynthia already mentioned, I will be talking

about the near national study using Medicaid analytic extract data and largely, for this presentation, focus on Type 2 diabetes as an outcome.

So I need to acknowledge, as was pointed out before, funding from AHRQ and FDA both to the Rutgers Centers for Education and Research on Therapeutics as well as specifically for this project. At AHRQ, we work closely with Chunliu Zhan, who is the project officer for this project. And at FDA, Cindy Kornegay and David Graham were some of the people I want to point out specifically, but others have been pointed out before, and I don't want to -- yes, I want to acknowledge them as well.

This study has a lot of collaboration and collaborators at Rutgers, the Institute for Health, Cecelia Huang, Ed Malka, and Stephen Crystal, who is the PI of the overall project as well as the Rutgers CERTS. Mark Olfson at Columbia University, Bill Bobo, Bill Cooper, and Wayne Ray at Vanderbilt University, and Christoph Correll at Zucker Hillside.

Just an important disclaimer here, this presentation really reflects preliminary findings of

ongoing work. We're close to finalizing this, but it's not a completely finished product at this point.

Just for a very brief background. So the background or the underlying rationale for this is the substantial increase in antipsychotic use that has been observed since the introduction of these second generation antipsychotics. So from the mid '90s to the early 2000s, probably an increase fivefold, if not more. That has in the mid 2000s kind of flattened off a little bit, but remained rather high.

Labeled indications for antipsychotic medication in this population, and that's even disregarding age groups and age limits, include schizophrenia and other psychoses, behavioral symptoms of autism, mixed and manic episodes of bipolar disorder, and Tourette's syndrome.

However, importantly, and you'll see this in these data that I will present, a large proportion of use is off-label. In prior work we have done and others have done, probably at least 50 percent of all antipsychotic use in youth is in children, adolescents that do not have any labeled indication. And a large majority of

those children have diagnoses of either attention deficit hyperactivity disorder and/or conduct disorder. So it's really a situation where symptomatic behavior is treated rather than a formal diagnosis.

These high observed treatment rates are of concern because of the metabolic and other adverse effects of the antipsychotic medications. We know from adults pretty clearly that there is substantial weight gain and an increased risk of diabetes, also of lipid abnormalities in adults.

There is also an FDA class warning regarding the risk of hyperglycemia and diabetes for second generation antipsychotics, and metabolic screening and monitoring is recommended for all the agents. And recent work by Christoph Correll and others has shown that specifically for weight gain, it seems that children and adolescents are actually maybe even at greater risk than adults or that the observed weight gain proportionally is actually larger in this population or in the population that really initiates newly an antipsychotic.

As for comparative metabolic effects, which is

really the focus of this study, we really have very limited data on the comparative metabolic effects of second generation antipsychotics. So there is some evidence from relatively short time observational studies that shows that olanzapine has greater weight gain than some of the other agents, although all of the agents show significant weight gain, and that also olanzapine looks pretty bad in terms of glucose and lipid parameters.

Potentially, some agents -- aripiprazole and ziprasidone -- may look slightly better, but the data is certainly not sufficient.

In adults, there is some observational data that suggests higher risk for olanzapine and potentially lower risk for aripiprazole for incident diabetes, but these are very preliminary findings that certainly come with a lot of limitations.

So the objective for this study was to estimate the comparative risk for incident Type 2 diabetes for individual second generation antipsychotic agents in publicly insured young people 6 to 24 years old.

Just a broad overview of the methods. So this is

a retrospective observational cohort study that uses near national Medicaid data. So this is data from 45 states, reflecting approximately 95 percent of the U.S. publicly insured population, and the data is from 2001, January 2001 to December 2005.

And again, importantly, this study examines comparative diabetes risk. So there's no comparison to nonusers of antipsychotic agents.

We used a new-user design to avoid bias from adjustment for intermediate variables and from depletion of susceptibles. So, basically, what this means is that we identify children/adolescents who start an antipsychotic agent, and I'll describe in just a second of how these were defined or how their start was operationalized, and follow these patients forward, very similar to the setting that would be used in a clinical trial, instead of including prevalent users that have been on the drug at the beginning of the study.

Because if we would include patients that have at the beginning of our study, the beginning of data availability already been on the agent, it's basically

impossible to distinguish when we adjust for covariates whether these variables had been already affected by the exposure. And in addition, any prevalent user cohort basically represents a cohort that is made up from basically survivors and patients that remained on the treatment largely because they did not experience any adverse effects. So it will underestimate any risk in this population.

We used a claims-based validated case definition for Type 2 diabetes, and as mentioned before, this claims definition was developed by our colleagues at Vanderbilt and then validated against medical charts. And I'll talk a little bit about this as well.

In terms of adjustment for confounders, given that this is an observational study, we basically adjust for everything that we can adjust for in claims data, which include socio-demographics and healthcare claims. And healthcare claims include basically diagnostic history, medication history, as well as history of service utilization.

As to our study population. So, as mentioned before, we have a new-user design. So our study

population is made up of new users of antipsychotic medications, and this was defined as no use of an antipsychotic medication at least 365 consecutive days that they were eligible for Medicaid so that we would observe any use of medications if it had occurred.

The first day of antipsychotic medication use is our index date, and an additional inclusion criterion was that the patients had to have at least 2 care encounters during the 365-day pre-index period. One had to be within a 90-day period before to assure that there was contact with the medical care system.

So if you have a subject that is not in contact with the medical care system, we basically wouldn't be able to observe any diagnoses because that patient wouldn't see -- have contact with the healthcare system, wouldn't see a physician. So that patient couldn't be diagnosed with anything.

There were several exclusion criteria. First and foremost, any diagnosis of diabetes or claim for an anti-diabetic medication in the 365-day pre-index period. A hospital stay during the 30 days prior to the index date because we basically do not have drug

data during hospital stays because that's basically lumped in with a capitated payment to the hospital. So it's not recorded in the Medicaid claims data.

A serious somatic illness, and those illnesses included cancer, HIV, dialysis, sickle cell disease, and a number of others, pregnancy and polycystic ovarian syndrome. All of these comorbidities were assessed in the 365-day pre-index period.

The exposure for this study was limited to the most commonly used antipsychotics -- risperidone, quetiapine, olanzapine, aripiprazole, and ziprasidone -- during our study period. However, the exclusion criteria were applied to all antipsychotics. So the initiators of any of these agents did not use any antipsychotic medications, not just these study medications.

We then constructed a calendar of antipsychotic medication exposure based on the days supply as recorded in the claims data. We didn't consider stockpiling. So if a patient filled a prescription early, we did not consider this, but rather started the -- or assessed the days supply based from this day on

forward.

However, we allowed breaks in days supply of up to 14 days to basically make up for the fact that some patients fill a prescription early and then fill the next prescription late while using the stockpiled medication. So if a patient had a break of more than 14 days and the index antipsychotic exposure was -- or that the patient was considered discontinued, and follow-up was censored.

For patients who discontinued their drug, we added 30 days to the last day of exposure in terms of follow-up time to minimize potential bias from informative censoring. So patients that would have, let's say, a very drastic weight gain or very drastic change in metabolic parameters, then discontinued the drug and then be diagnosed with diabetes, we want to avoid the situation that these cases of diabetes would not be counted. So we add 30 days to the end of follow-up, and we have alternative specifications for this in sensitivity analysis.

As for the endpoint, the computer case definition was developed at Vanderbilt. Basically, users'

diabetes-related medical care encounters, and there are four types -- an inpatient primary diagnosis, an inpatient secondary diagnosis, an outpatient diagnosis, and the prescription of an anti-diabetic medication.

The first, the inpatient primary diagnosis, in and of itself, is sufficient to meet the case definition. The other three encounter types basically require confirmation within 120 days following that date by one of the other criteria.

So if there was a patient with an inpatient secondary diagnosis, this diagnosis, in and of itself, does not meet the criteria for diabetes. In order to meet the case definition, there needs to be either an inpatient primary diagnosis, an outpatient diagnosis, or a prescription for an anti-diabetic medication in the following 120 days.

The event date is then the first date of the first encounter, but it is recoded if a diagnostic procedure is observed within the previous 30 days because then that, presumably, is a more close approximation of the first date of the disease onset.

The distinction between Type 1 and Type 2 diabetes

from claims was made as follows. So, basically, Type 2 diabetes was that the patient was considered a Type 2 diabetic unless he had one or more claims for insulin and less than two claims for an oral hypoglycemic medication within 120 days.

Confounding adjustment was based on covariates assessed during the 365-day pre-index period. Again, since we required 365 days of eligibility without an observed antipsychotic medication, we had this time period to be able to collect a wealth of confounding information from claims.

We constructed eight socio-demographic variables. So that's basically age, sex, race, ethnicity, as well as Medicaid eligibility categories. A lot of this work is actually based on work by our colleagues at Vanderbilt and basically includes 77 diagnostic categories from claims, 45 medication classes recorded from claims, and 10 variables describing the utilization history.

So this is things like the number of days in the hospital in the previous 365 days or the number of outpatient visits in different time periods in the year

prior to the index date.

Adjustment was then done using propensity scores. So we did -- modeled propensity scores using nonparsimonious logistic regression models for each index antipsychotic compared to risperidone. So these are all binary comparisons to risperidone. And risperidone was chosen as the comparator because it's the most widely used agent.

We trimmed the low and the high end of the distribution of the propensity scores and included then the deciles of the propensity scores of the trimmed propensity score distribution into the outcome models. For some of the subgroup analyses that I'll show, we included quintiles just because the number of events was really low, and that gave more stable results. And for subgroup analyses, we calculated propensity score models for each of the subgroups.

Here is just a quick display of the propensity score distributions for the full cohort. And basically, you see here that based on the variables that we have from claims observed in the -- observed from claims and included in the propensity score model,

there is very good overlap between the two groups.

So we have always in red risperidone and in blue the other agent. There is a lot of overlap between the groups. Usually propensity score adjustment is problematic when these distributions do not overlaps.

We did some descriptive analyses that I will show, but the main analysis model is a Cox proportional hazard regression, so the time to either censoring or development of diabetes.

Basically, we did an "as treated" analysis that censored patients at discontinuation of the index medication; at the addition of a second antipsychotic medication, regardless of whether this was an addition of a second agent or a switch or cross titration; the day prior to the 25th birthday; lack of medical care encounters; pregnancy; polycystic ovarian syndrome; development of a serious somatic illness; Type 1 diabetes; and basically then the end of the study dataset, the date of death and the loss of eligibility.

For the latter three, we basically censored 120 days prior to these events because our outcome definition requires confirmation within 120 days. So

we need to make sure that we censor patients once this window is not available for confirmation for every patient, or for the full period.

Sensitivity analyses were conducted for different exposure definitions. So instead of adding 30 days of follow-up after discontinuation, we added 90 days in the sensitivity analysis. In a second sensitivity analysis, we also added 30 days not only to the patients who discontinued, but also to those who switched or added a second medication. And in a third sensitivity analysis, we added no days of follow-up.

Subgroup analyses were done by age group, sex, antipsychotic medication indication and dose. The dose cutoffs were computed for both the index dose and the last observed dose. And the cutoff chosen was 75 milligrams chlorpromazine equivalents. The conversion that we used for each of the agents was the one proposed by Andreasen in 2010, and the cutoff point reflects the median dose for all the study antipsychotics.

We also conducted dose-response analysis, where we constructed tertiles for each agent individually and

then compared medium dose to low dose and high dose to low dose within each drug.

So, to the results. In terms of the endpoint validation, these data were validated in a 15-county area in Tennessee. Within that area, 64 cases met the computer case definition, and basically, this was in a cohort that's used in the ongoing kind of sister study that's being performed right now at Vanderbilt.

Sixty-four cases met the computer case definition. Records could be retrieved for 46 of these cases, and those cases were independently adjudicated by 2 investigators.

The computer case definition has a positive predictive value of 89.1 percent. So 41 of 46 cases were adjudicated as definite or probable. Three of the five cases that were not adjudicated as definite or probable were sub-threshold hyperglycemia. One was a prevalent case of diabetes, and one was a case of polycystic ovarian syndrome.

And the sensitivity is more of an estimate based on a sample of the non-cases was estimated at 64.8 percent. As for the distinction between Type 2 and

Type 1 diabetes, 31 cases were classified as Type 2. Twenty-three of those were adjudicated as Type 2, 3 as unknown type, 1 as Type 1, and 4 are these previously described cases of not incident diabetes.

Overall, the study population consists of 161,559 youth with a mean age of 12.6 years. Sixty-four percent of the study population was male.

We had a total follow-up time of 55,140 patient-years, and from that, you can already see that the follow-up time is very short. So a mean follow-up of 125 days, with a median of 73 days, basically reflective of the observed pattern in this setting that antipsychotics are discontinued very, very frequently and very quickly.

In terms of the reason or for the end of the follow-up period, more than 70 percent are due to discontinuation. A much smaller proportion due to loss of eligibility or the end of the study period, and even smaller proportion for addition of a second antipsychotic or switching or any of the other censoring reasons.

We had a total of 309 cases of diabetes, 289 cases

of Type 2 diabetes. The mean time to event was 63 days, with a median of 46. Incidence of diabetes was 5.6 per 1,000 patient-years, and incidence of Type 2 diabetes 5.2 per 1,000 patient-years.

As for the descriptives here, this slide just shows the age, sex, race, ethnicity, as well as the mean follow-up time, the median follow-up time, and the index dose in chlorpromazine equivalents. We certainly observed some differences between the drugs. Specifically, actually, basically all drugs looked somewhat different than risperidone, which is the comparator.

Risperidone patients were the youngest and most male population. There are some differences in race/ethnicity as well. However, risperidone patients have the longest follow-up, and there are also certainly differences in the index dose after conversion to chlorpromazine equivalents, where risperidone and quetiapine are given at lower doses than olanzapine, aripiprazole, and ziprasidone.

When it comes to mental health characteristics, again, risperidone is a little bit the outlier here.

Actually, I forgot to mention in the last slide or in the overall, about half of our patients were initiated on risperidone, 81,984; 33,600 on quetiapine; 25,000 on olanzapine; 15,600 on aripiprazole; and only around 5,000 on ziprasidone.

For the mental health characteristics, so the mental health diagnostic history and psychotropic medication treatment history over the 365 days pre-index, risperidone patients seem to be less severely ill with a lower proportion of combined schizophrenia and bipolar disorder, a higher proportion of PDD or mental retardation, higher proportion of ADHD and conduct disorder, and a lower proportion of depression and anxiety disorder, with ziprasidone kind of being on the other extreme end with the largest proportion of schizophrenia and bipolar disorder.

Similar patterns with some differences in the concomitant -- or not concomitant, but with psychopharmacological treatment during the baseline period.

Also important to find out while we didn't specifically assess whether any of these treatments

were used concomitantly, these data strongly suggest that we'll have a lot of psychotropic polypharmacy. A lot of these children/adolescents are not only taking an antipsychotic, but also an antidepressant, ADHD drugs, an anxiolytic, and/or mood stabilizer.

This slide basically compares the baseline metabolic characteristics observed from claims, and I think this slide very much illustrates the big weakness of this study and the one thing that is basically the biggest discussion item that we'll be getting to that, unfortunately, claims data are not doing a very good job in recording metabolic baseline characteristics. So we are obviously not having a BMI recorded or any lab values recorded. What we have are diagnoses or tests.

So when we look at obesity, whether morbid or non-morbid, we see very low rates, much lower than actually common in the overall adolescent and child population, although we know that these rates are actually higher in the population with psychotropic comorbidities. So it's clear that these diagnoses for obesity are underdiagnosed.

Nonetheless, we find some differences between drugs where, for example, patients with risperidone and olanzapine have lower rates of obesity than ziprasidone, which may only not be indicative of differences in true obesity rates or true differences in baseline BMI and other metabolic parameters.

Baseline characteristics regarding healthcare utilization look very similar across drugs. So it's basically in different time periods, the number of outpatient visits, emergency department visits, and days in the hospital. And there are basically no differences observed.

As to the outcomes, so we see here for risperidone, 120 incident cases in 30,520 person-years, resulting in an incidence rate of around 4 per 1,000 patient-years. And basically, this incident rate is increasing for quetiapine, aripiprazole, olanzapine, and ziprasidone. For ziprasidone, quite significantly higher at 11 per 1,000 patient-years.

Also show here the mean and the median times to events in each of the groups, and there are some differences in each of the drugs, and there are some

differences.

So when we now look at the time to event analysis, we see that the unadjusted results obviously reflect what I've just shown in the incidence rates with higher hazard ratios for quetiapine, aripiprazole, olanzapine, and ziprasidone, ranging going up to around 2.7 for ziprasidone. However, even -- and if we go now to the right, we basically add additional stages of adjustment where the first is basically just an adjustment for sex, age, race, and index year, and the second is basically the full propensity score adjusted model.

We see that the adjustment basically moves all estimates towards the null, so much smaller differences in risk. And that is true for all drugs compared to risperidone. We also see that the vast majority of this adjustment is already done with the demographic adjustment, and largely, this is actually the age adjustment when you look at the individual variables.

Where we finally get to propensity scores, a fully adjusted estimate shows nonsignificantly higher point estimates for quetiapine, olanzapine, and aripiprazole, as well as ziprasidone. But we see that, for example,

the unadjusted estimate of 2.7 is going down quite significantly to 1.44.

However, in this context, it's probably a good time to mention this first, and I'll get back to this. It is unclear to what extent these findings reflect now differences in baseline differences of unobserved variables like the BMI, other metabolic parameters. So they're certainly not fully conclusive.

The next two slides basically just show the results not for Type 2 diabetes, but for diabetes overall. And they're basically, since we have 289 Type 2 diabetes cases and 309 diabetes cases, largely identical to what we see for Type 2 diabetes only.

Now the results for the sensitivity and stratified analyses. So this slide basically looks at the different exposure definitions, whether we add 30 days to the end of -- after discontinuation, add this to the follow-up as an exposure risk window, whether we add 90 days, whether we add 30 days for discontinuation as well as switch or whether we don't add any days. And we find very consistent results across these different specifications.

If we stratify, we don't see much of an effect of stratification by age. However, you see kind of the point estimates moving around here a little bit. So for quetiapine, for example, the lowest age range is 1.39. The mid age range, 13 to 17, 1.11. The highest, 18 to 24, age range, 0.93. So they start to look a little different. But if you look at the confidence intervals, they all clearly overlap.

So the test to see whether there's an actual difference in the effect by stratum would be that the confidence intervals don't overlap. And clearly, we don't see any of this for some. We have the point estimates moving around, but we also get into really small numbers. So that's not surprising.

Very similar findings when we do the stratification by sex. We also wouldn't expect a difference, and we don't see it.

For antipsychotic indication, a similar finding, basically overlapping for confidence intervals across strata.

When we look at dose response, we basically don't see a big effect for risperidone, quetiapine, or

aripiprazole. Ziprasidone really doesn't have the numbers to do this internal dose response because there are just too few diabetes cases in ziprasidone users, too small of a study group.

And then seems to be a weak signal for olanzapine that it both shows for the high versus low and medium versus low an increased risk. However, we also did -- this is not adjusted for multiple comparisons. We also did a lot of tests here. So I would not interpret this as more than a weak signal.

It's also important to note that this dose response, even within drug comparison, may very well be confounded by baseline risk, baseline BMI that children with already a high kind of metabolic baseline risk may be more likely to be initiated on lower doses. So there might be some underestimation of the dose-response effect.

The previous slide looked at the dose response by the index dose, while this slide looks at the dose response based on the last dose, basically making the assumption that the last dose is closer to the actual dose causing the outcome. It's always very problematic

to adjust for something that happened after baseline. So this is really an exploratory kind of analysis.

Overall, about 70 percent -- and this was very surprising to some of our collaborators. About 70 percent of children/adolescents remained on the same dose throughout follow-up so that they did not titrate the dose in any way. Which is surprising even though the follow-up period is obviously very short, and for most patients it's only one, two, three, four scripts. But still, many people I talked to had expected a much higher proportion of children that had a titration end dose.

The only thing I want to point out here based on the last dose is really that the olanzapine result is kind of consistent. It's the both higher doses for olanzapine show kind of an increased risk compared to the lowest dose range of olanzapine.

And the reduced risks that you see here for the last dose very well and for some of the other drugs -- so high versus low, for example, for risperidone or high versus low for aripiprazole -- very well may reflect this idea that it's less likely for children

that have a strong response in terms of weight gain and other metabolic changes, they are less likely to actually have a dose that's increased. So this might be just an artifact of dosing that's actually reflective of observed metabolic changes over follow-up.

Given what we've seen in terms of dose response, we kind of can expect or can already kind of foresee what we see here in terms of dose stratification where we just make comparisons between the individual drugs to risperidone either in patients that had 75 milligram or less in chlorpromazine equivalents or a higher dose where we really don't see much for quetiapine, aripiprazole, or ziprasidone. The only drug where we really saw a difference -- dose response or had some signal for dose response, olanzapine, therefore, then also looks worse when we limit the analyses to those with a high dose.

But again, like I said for the dose response, again, this is, I would say, a signal as something interesting to follow up and certainly not a confirmation. And again, these findings are

consistent, kind of the effect of olanzapine at the high dose is consistent when we do this only based on the last dose.

The last results slide that I have here is really a fully exploratory analysis that even the stratifications to some extent were more exploratory and hypothesis generating. This certainly is even more, but it addresses the issue could it be -- that we didn't detect any difference between agents, could this be due to the fact that we just didn't have enough follow-up time?

That it just takes longer for diabetes to develop, and given that the vast majority of patients have such short follow-up, the true effect differences may just be drowned out?

And so, here we restricted the cohort to those who remained on their index antipsychotic for -- and were not censored for other reasons for more than 90 days, 180 days, and for more than 365 days. So what you obviously see is a pretty dramatically reduced number of subjects in each of the groups. And obviously, it is very important to acknowledge that there are

potentially very strong selection effects that may bias these results because we now limit the analyses to those who remained on the drug for long periods of time.

However, and so, with all these caveats, we see kind of what appears to be a trend for olanzapine that when we restrict it to patients with longer follow-up, the risk of olanzapine compared to risperidone for Type 2 diabetes seems to increase. Again, very much to be seen in the context of hypothesis generation for future work, something that's in line with some of the things we know about the timeframe it takes to develop diabetes but, certainly, having quite a few limitations from kind of an epidemiological perspective.

So, in summary, again, this study aims to inform antipsychotic choice, not initiation. We have no nonuse comparison. Looking just at the results, as observed, we really see no evidence of significant differences in Type 2 diabetes risk between individual antipsychotic medications, and this finding was really stable across sensitivity analysis and exposure definitions.

We find no evidence of effect modification by age group, sex, or antipsychotic medication indication. We find not much evidence of dose response. There is this weak signal for olanzapine. We don't find evidence of effect modification by dose. Again, a weak signal for potential effect of olanzapine at higher doses. And we again see this potential signal for higher olanzapine risk when the analyses are limited to patients with longer follow-up durations.

However, in terms of limitations, and the first one should really be bold, there is a strong potential for residual confounding by BMI, metabolic parameters, family history, that are all unobserved in our claims data.

The other one that I would consider very strong limitation, not necessarily of this study but of the way antipsychotic treatment occurs in the population, is this limited duration of follow-up due to early antipsychotic medication discontinuation. So that's not a flaw of the study. That's just how treatment occurs in practice.

So if we want to evaluate the effects of

medications on diseases that take -- potentially have a long duration of onset where these exposures are very short and very likely to be discontinued because of intermediate metabolic changes, that's just in general just a very difficult study question to answer for any type of study design. That wouldn't be different in a clinical trial. Those discontinuation rates would make it very difficult to get good results from a clinical trial, not even talking about the issues with sample size.

Obviously, the other limitations of kind of a claims-based cohort study apply. We have a potential for outcome misclassification. Although we used this claims-based definition that was validated, we have a potential for exposure misclassification, particularly in those patients that only had a single prescription for an antipsychotic medication in that we really don't know whether they took the full duration of exposure. It's actually somewhat unlikely that they did. We don't even know whether they took any of that medication. Those are probably limitations that should bias results toward the null.

Dose analyses were based either on the index or on the last dose. Both have their disadvantages. We clearly have this potential of selection bias in analyses restricted to patients with longer follow-up durations.

So, in conclusion, if I had to summarize the findings of the study in one sentence, I would say the results are inconclusive. The failure to detect differences in Type 2 diabetes risk between individual agents while, first of all, that may be true. There may not be differences, but that also may be due to although this is a very large study, we still have a very small number of cases of incident Type 2 diabetes. So we have small numbers.

We have a high potential for residual confounding due to channeling of high-risk patients to agents perceived to have less metabolic effects. And we have, as discussed before, the short follow-up duration resulting from the early discontinuation of antipsychotic medications.

So future work should aim to, well, increase sample size and follow-up duration. So that's actually

a pretty straightforward process, given that the data ended -- for this study ended in 2005. There is much newer data available. So the study may be extended to include more recent data.

More importantly, I believe the challenge will be to integrate BMI and metabolic parameters to improve confounding adjustment. There may be an opportunity to use automated data resources from health plans, for example, that have lab data, electronic medical records, and some of these BMI, weight, height coded to allow the integration of these values in confounding adjustment either as a full study or as kind of a calibration in a subsample.

And if these data were available, some metabolic values -- BMI and so on -- one could also explore the feasibility of having longitudinal follow-up, examining longitudinal changes in these parameters in larger populations rather than just small, observational prospective studies that I believe most of the current evidence is based on.

And I'm happy to take any questions.

DR. ROSENTHAL: Thank you for your presentation.

We actually have a few minutes for questions for Dr. Gerhard, and also for Drs. Cope or Kornegay if people have them?

Yes, Dr. Wagener, I saw your hand up?

DR. WAGENER: So, generally, when I think of a chronic illness, I would expect patients to be kept on a medication chronically. And the short duration is interesting in this.

I guess I wondered if you've theorized, do you think that the short duration of therapy might have been related to the development of adverse effects, or is it because over 50 percent of the doses are being given for ADHD, a nonindicated use, in which case they may only be treating during the school year and stopping the drug early for that reason?

DR. GERHARD: So I think there are kind of a couple of questions. I think there is certainly -- first of all, the data on follow-up duration and time to discontinuation I think are very consistent with what we see in clinical trials, very high discontinuation rates for the antipsychotics.

I think, given the observed weight gain and so on,

I think probably a large -- and this is really speculation. I have nothing, no data to base this on. But I think it's very likely that a lot of this comes from the pretty immediately observable metabolic effects, especially the weight gain. On the other hand, it may also be a lack of perceived effectiveness in either the indicated conditions, but also in the nonindicated conditions.

In the group with ADHD, I don't expect kind of the pattern that we know from the stimulants, that treatment occurs in the school year, not so much -- and then it's kind of there are breaks in the summer. I think while these children have a diagnosis of ADHD and/or conduct disorder, I think what's actually treated and there is some evidence from prior work that we have that their treatment is less for kind of symptoms of ADHD, but much more for the symptom of aggression, aggressive behavior.

I'm not so sure whether that would be limited to only the school year. I think these are just children that can't be managed and where it's seen as one thing to try. And very likely -- or neither of these drugs

have a clear indication for it. So in this use, there might not be an immediately observable benefit. So an early discontinuation wouldn't be very surprising.

DR. WAGENER: Have you separated out the ADHD patients and looked at them as a subpopulation to see if they -- how they compare with the overall population?

DR. GERHARD: Well, we did in terms of the result. This was the subgroup analysis for indication versus not, where basically the no indication part is basically that population. I didn't show the descriptives here, but they will look somewhat different.

DR. ROSENTHAL: Yes. And do you mind just introducing yourself to the table?

DR. LAUGHREN: Okay. Don't hold it here? Okay.

Tom Laughren. I'm the director of the Division of Psychiatry Products at FDA.

This was a heroic study to try and get at something that's very difficult to get at, and it's the only way to look at an event like Type 2 diabetes. You're not going to get at that in any controlled

trial, even though a randomized controlled trial would get around the major problem that I think you've identified in this trial, which is differential prescribing, based on the patient's either baseline status.

And adjusting, getting data on weight and BMI at baseline would help, but it may not completely solve the problem because a thoughtful clinician might also rely on family history. If there's family history of Type 2 diabetes, they may differentially prescribe based on that, even though that's -- the child at baseline doesn't have abnormal metabolic parameters.

One other thought is that this was a retrospective cohort study. Correct? So has there been any thought to doing a prospective cohort study? Again, you're never going to get randomization to look at an event like this. But if you prospectively collected good data at baseline on weight, BMI, family history, that might give you a better chance of at least adjusting for the differential prescribing that you see.

DR. GERHARD: I completely agree with basically all of your comments. I don't think that a truly

prospective study with active data collection is really feasible given the numbers that we need. But I think potentially using even whether the data is retrospective or prospective doesn't even matter.

But not using active data collection, but using data that may be available in electronic medical records, for example, that would potentially -- and obviously, that has problems -- potentially even allow assessment of recorded family history may be an approach.

The other issue I think that I would want to point out is that depending on how the results turn out, I think it's easier or harder to deal with, to interpret results that may still be confounded. So if a drug that is likely to be rather reserved for the sickest patients, the patients with the highest baseline risk after all adjustment, already looks protective even though we cannot fully adjust for all these baseline differences. I think there would be a strong rationale to use this information and recommend this drug.

In our instance, the way the results turned out that the drugs that would be suspected to be kind of

reserved for the sickest patients, if they turn out nonsignificantly worse, that really makes it very hard to come to any kind of conclusion from the results.

DR. LAUGHREN: Striking when you look at the way the risk ratios line up, it's just completely the opposite of what you see in controlled trials. I mean, nothing really has changed since the CATIE study was published 6 years ago and these same drugs were looked at. And the way they lined up is that olanzapine was the worst, then came quetiapine, risperidone, aripiprazole, and finally, ziprasidone.

And in your results, ziprasidone had the highest risk ratio, and aripiprazole was next when they're -- if you look at them certainly in a controlled setting, a randomized controlled setting, they fall at the other end. And all the data that we have from controlled trials, both adult and pediatric, suggest basically the same thing.

DR. GERHARD: I completely agree. But I would expect that if the just baseline BMI and lab data would be integrated, this would look already very different, although I would acknowledge that, even then, it

wouldn't be perfectly adjusted. It would be at least interesting to see.

DR. ROSENTHAL: Other questions or comments from the committee?

(No response.)

DR. ROSENTHAL: All right. Thank you very much.

DR. GERHARD: Thank you.

DR. MURPHY: Yes. I really do want to take an opportunity to thank Dr. Gerhard, Dr. Crystal. This is just -- we've been struggling, as this committee knows, trying to get better data on this issue. And this was a heroic effort and appreciate AHRQ's contribution to -- financially to help us do this.

And Tom, I don't know. We just keep sort of circling in, but we can't get to some sort of definitive conclusions on this. But we did want to bring it back to the committee. It takes a while, but we do try to follow up on all your recommendations, and this is where we are at this point in time.

DR. LAUGHREN: If I could make a plug that I've made in the past? We have this very nice CATIE study in adults that does a head-to-head comparison of all

five of these drugs. It would be nice to have a CATIE for kids that basically did the same thing. That would at least help us with looking at common metabolic measures like weight and lipids and glucose and so forth.

DR. ROSENTHAL: Yes. Dr. McMahon?

DR. MCMAHON: I was just going to ask, and if you did have such a study, how long would you follow up the patients?

DR. LAUGHREN: Well, of course, that is a serious problem. I mean, we obviously can't get long-term, placebo-controlled, head-to-head study. Now you could do an active control study that just looks at active drugs and follow kids for as long as they'll take them.

I mean, the problem with all of these studies is that even in a controlled trial, patients drop out fairly abruptly. You certainly saw that in CATIE. But you would at least there have some chance of getting longer-term data.

DR. MURPHY: And I don't think this is the end of the story yet. I do think that we are going to try internally -- it's not definitive -- try to look at

some weight, BMI and weight, if you want to talk a little bit about that, Ann?

DR. MCMAHON: Well, I mean, there is an effort ongoing to do a next phase, which I think Dr. Gerhard alluded to, to using weights as baseline and continuing this effort through claims data. It isn't definitive yet, but --

DR. MURPHY: It certainly does take care of the problem of few cases of Type 2 diabetes, Type 1. You know, if your measurement is going to be changes in weight as one of the --

DR. ROSENTHAL: Yes, Dr. Wagener?

DR. WAGENER: So I actually was fairly concerned with how high the number of diabetes cases was. How does this compare with the adult? And if, indeed, it's higher than typically seen in the adult population, is there an effort to add to or modify the package inserts that express this concern?

And then, finally, what was impressive about the diabetes is that it's developing at such a rapid onset. So this is not a long-term complication. This is a short-term complication of this drug. Is that the case

in the adult population?

DR. LAUGHREN: Let me ask that I think that the rate was 5 per 1,000? How does that compare with the background rate in adolescents these days?

DR. WAGENER: In 60 days, that's way above the background rate. This happened 60 days from enrollment, there were 5 per 1,000 patient-years predicted.

DR. LAUGHREN: We don't -- at least not that I'm aware of, we don't have similar cohort data for adults, I don't think. I mean, all we have are spontaneous reports. Now someone may know of a similar study in adults. I'm not aware of it.

DR. MURPHY: I don't know of a similar study in adults, but I agree. We just got this data, and the thing that struck me was the 45 to 60 days. And when we looked at some of the adverse event cases for weight, it was happening, some enormous weight gain in short periods of time.

So that's why we're here. We're trying to decipher out. And what we're stuck with is even though it was 62 cases is a lot, it's still not going to give

you the power that you need to be able to do any differentiation. And I think that's why we're still plugging away.

We'd like to have a CATIE study. We're going to try to go and look, get some data where we have weight because that takes care of one issue, but also it enters into some others, you know, which is measuring that. But the bottom line, I think, on our answer to all of this is that we're continuing to try to find ways to address this issue.

DR. ROSENTHAL: And just to be clear in terms of the time element in the denominator, the incidence that was just reported was 5.6 per 1,000 person-years. So, all right.

Other questions or points?

(No response.)

DR. ROSENTHAL: All right. Well, very good.

Thank you for circling back and for helping us to revisit this question.

Our next speaker is Dr. Amy Taylor, who is a medical officer in the Pediatric and Maternal Health Staff in the Office of New Drugs in CDER. And Dr.

Taylor will be talking to us about aripiprazole.

And this will be a pediatric focused safety review. So we're transitioning into other work of the committee at this point.

DR. TAYLOR: Thank you, and good afternoon.

As was said, I will be presenting the safety review for Abilify. This outline gives the topics that I will cover in my presentation.

Abilify, or aripiprazole, is an atypical antipsychotic marketed by Otsuka Pharmaceuticals and Bristol-Myers Squibb. There are three oral formulations and one injectable formulation.

Abilify is indicated for treatment of irritability associated with autistic disorder. Studies were in patients age 6 to 17 years. It is also indicated for the treatment of schizophrenia. The studies were in patients age 13 years and older.

Acute treatment of manic or mixed episodes associated with bipolar I disorders as monotherapy and as adjunct to lithium or valproate. The studies were in patients age 10 years and older.

Maintenance treatment of bipolar I disorder, both

as monotherapy and as an adjunct to lithium or valproate. The studies were in adults. Adjunctive treatment of major depressive disorders. The studies were in adults.

And the injectable formulation is indicated for acute treatment of agitation associated with schizophrenia or bipolar disorders, and these studies were in adults.

Abilify received its original market approval on November 15, 2002, and was granted pediatric exclusivity on November 14, 2007. The PREA labeling changes related to this presentation were approved on November 19, 2009. The labeling changes are related to the treatment of irritability associated with autistic disorder.

With regards to that indication, Abilify was studied in two 8-week placebo-controlled trials in pediatric patients age 6 to 17 years with autistic disorder and demonstrated behavior such as tantrums, aggression, self-injurious behavior, or a combination. The primary endpoint was a change from baseline to endpoint in the irritability subscale of the ABC. Of

note, the clinical global impression improvement scale was also used for assessment.

In the first study, patients demonstrated significantly improved scores on the ABC-I subscale and the CGI subscale compared with placebo. In the second study, there were significant improved scores on the ABC-I subscale compared with placebo at all dose levels.

This table shows the commonly observed adverse reactions.

These studies resulted in changes in the Dosage and Administration, Adverse Reactions, and Clinical Studies sections of Abilify labeling. The next four slides will discuss the safety labeling relevant to pediatrics. There is a boxed warning for the risk of suicidal thinking and behavior.

In the Warning and Precautions section of labeling, there is a discussion of suicidality and antidepressants, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, and diabetes mellitus. Orthostatic hypotension, leukopenia, neutropenia, and agranulocytosis, seizures,

convulsions, the potential for cognitive and motor impairment, difficulty with body temperature regulation, and suicide.

Between November 2009 and March 2011, 9.7 million prescriptions and 1.9 million patients were dispensed prescriptions for aripiprazole. 1.9 million prescriptions with 369,000 patients were for patients 0 to 17 years old. Eleven percent of prescriptions were for 13- to 17-year-olds, 8 percent for 7- to 12-year-olds, and 1 percent for 3- to 6-year-olds.

The top prescribing specialty for aripiprazole prescriptions was psychiatry at 62 percent. Pediatricians accounted for 2 percent of aripiprazole prescriptions.

The top diagnosis code in pediatric patients age 3 to 6 years and 13 to 17 years was bipolar disorder. The top diagnosis code in pediatric patients age 7 to 12 years was affective disorder.

In December 2009, an Abilify safety review was presented to this committee. The committee recommended at that time additional information on weight gain be added to labeling. FDA is and will be reviewing

additional data regarding pediatric metabolic adverse events related to the use of atypical antipsychotics.

The committee also discussed concerns about the use of atypical antipsychotics in ADHD, and the committee requested FDA review use data associated with a diagnosis of ADHD without other coexisting diagnoses.

This table shows the crude count adverse events. There were 438 total pediatric reports, 193 of which were serious, and there were 7 cases of death. Of the 193 cases, 164 were unduplicated cases. Two cases were miscoded, which left 162 cases which were reviewed, and these include the 7 cases of death.

This slide shows demographic information of the pediatric cases reviewed, giving gender and ages. And this slide shows dosing and duration information.

There were seven cases with an outcome of death. The first case is a 10-year-old male who died of multiple organ system failure due to or as a consequence of ischemic cardiomyopathy, coronary artery stenosis, and congenital heart disease. He was on aripiprazole for 2 years but discontinued the drug 1 month prior to his death.

The second case is a 13-year-old male with bipolar disorder, had a seizure while on aripiprazole therapy for about a week. The patient died after an unspecified period of time, and the cause of death was not reported.

The third case is a 14-year-old male who died with symptoms of possible abscessed wisdom teeth consisting of headache, tooth and jaw pain, and possible fever. The patient was on aripiprazole as well as several other drugs, which are listed here. The autopsy report indicated an elevated tryptase level but stated that the reporter "could not rule in or rule out anaphylaxis."

There were four cases of in utero exposure to aripiprazole, including a set of twins, and no trend was noted. The first three cases are described here, and this is the fourth case.

I will now review the serious nonfatal adverse events. There were 155 cases reviewed, and you can see here a grouping of these cases. Unlabeled adverse events will be underlined, and each case may have multiple events.

There were 27 cases with extrapyramidal symptoms including dystonia, Parkinsonism, tardive dyskinesia-like symptoms, and unspecified EPS. There were two cases with motor disturbances.

There were 16 cases of metabolic adverse events. There were nine cases of weight gain, and this table shows the details of the cases of weight gain. The blank fields represent information omitted from the AERS report by the reporter.

There were three cases each of diabetes and metabolic changes, and there was one case of glucose abnormality. There were 20 cases of in utero exposure, and no trend in adverse events was noted. There were seven cases of accidental exposure and two cases of lethargy and somnolence.

The next eight slides list the adverse events grouped as miscellaneous. The events are organized by system organ class. The classes with the most events were psychiatric and nervous system.

Because you are able to read these, I won't go through the list and bore you with reading each adverse event. But you can see there that gastrointestinal,

there were four cases; hepatobiliary, four; cardiac, three; blood and lymphatic system, three; investigations, three; eye disorders, three; general, two; renal and urinary, two; skin and subcutaneous, two; vascular, two; and then one each of musculoskeletal and connective tissue, neoplasm, endocrine, infectious and infestation, injury, poisoning, and procedural complications, immune system, reproductive system, and then multiple diagnoses.

This concludes the pediatric focused safety review. No new safety signals were identified.

FDA recommends continuing routine ongoing post-marketing safety monitoring. Does the committee concur?

And I'd like to acknowledge the people listed here and thank them for their help with this presentation.

DR. ROSENTHAL: Thank you, Dr. Taylor.

The floor is open for questions, discussion, reflections.

Yes, Dr. D'Angio, and then Dr. Vaida.

DR. D'ANGIO: One question for you, Dr. Taylor. On the cardiac adverse events, I noticed that there was

a case of bundle branch block. Was that just one case? Do you remember?

DR. TAYLOR: Yes, it was just one case.

DR. D'ANGIO: Thank you.

DR. VAIDA: With the prescribing that you had on slide 15, you were saying that the psychiatry was 62 percent. How does that compare with prior, the prior report? Is that like a lot lower? Like, is the drug being prescribed more out of the psychiatry reign?

DR. TAYLOR: Well, one thing, and I would ask the use reviewer to confirm this, but this would be of all prescriptions, adult and pediatric, not just pediatric. So I'm not sure if that changes your question or not.

DR. VAIDA: Okay. Yes. Yes, it does.

DR. TAYLOR: Okay.

DR. VAIDA: I thought it was pediatric.

DR. ROSENTHAL: But the essence of your question is, is aripiprazole increasingly being prescribed by providers who are outside of the specialty of psychiatry? That's your question?

DR. VAIDA: Correct.

DR. TAYLOR: And I don't have the information from

the 2009 on what the top prescribing was. I'm not sure if anybody else has that, but I don't have it right here.

DR. VAIDA: I think I remember it was a lot higher.

DR. MCMAHON: Our people, our epidemiologists are coming to the microphone.

DR. ROSENTHAL: It would be okay for you to come up to the table, too, if you'd like.

DR. GOVERNALE: Laura Governale, Office of Surveillance and Epidemiology.

So Dr. Taylor was correct that when we looked at the prescribing specialty for aripiprazole, we are looking at both adult and pediatric populations together. We do note that the use of aripiprazole in the pediatric population is also increasing, but it's kind of plateaued in recent years.

DR. ROSENTHAL: Dr. Dure?

DR. DURE: I have so many things. Actually, I think the data, though, on who's prescribing through the years is on page 14 of the second or the use handout that we got. But I guess I have a real short

question, and then I want to -- I have a comment.

And I guess I'm curious, and maybe this has just passed me in the past, but these are called "serious adverse event, nonfatal adverse events." For some reason, I thought that serious referred to things that put you in the hospital, that sort of -- can you define "serious?"

DR. MURPHY: You're right. Serious is that you've either been hospitalized, you have a permanent paralyzing -- what am I forgetting here, Ann?

DR. MCMAHON: Death.

(Crosstalk.)

DR. DURE: Death, maiming?

DR. MURPHY: Yes. Any debilitating, yes.

DR. DURE: But on the slides here, a lot of these --

DR. MURPHY: Requiring an intervention.

DR. DURE: Yes. So, requiring an intervention? Okay. I still have problems with -- and I understand and I appreciate the position that the FDA is in, in trying to gather data for us. But I think this committee, I said it and some other people said it 3

years ago, you have data from clinical trials that show that anywhere from 30 to 40 percent of children have extrapyramidal side effects when they take Abilify.

Subsequent to that, there have been the studies from Correll that show -- and others that show that even naive children who take atypical antipsychotics, there is substantial weight gain. Can we not include that in the label? I mean, you're including data from clinical studies that are supplied by the sponsor, but how about other data that is germane?

DR. LAUGHREN: We are in the process of finalizing the metabolic section of the label for aripiprazole, and that should be out within a month to 6 weeks, that will provide very detailed information about -- but again, it's focused on the data that we have access to, which is the data from the clinical trials, both adult and pediatric. All of those data are going to be put into the Warnings and Precautions section, even though the different drugs have very different profiles.

The profile that we're seeing for aripiprazole in the controlled trials that we've looked at, both adult and pediatric, are not nearly as alarming as what you

see with olanzapine. Olanzapine really stands out. And then it really -- we're seeing very similar data to what you saw in CATIE where some drugs fall sort of in the middle -- quetiapine, risperidone -- and then aripiprazole and ziprasidone are at the other end.

They all have a signal. They all cause or are associated with some weight gain, you know, some metabolic changes, but really quite modest.

Now these are short-term studies. These are 4- to 6-week trials.

DR. DURE: But 2 kilograms a week in a 6-year-old or in a month in a 6-year-old is very different from a 45-year-old. So is there no -- is there not any distinction made there?

DR. LAUGHREN: We're not seeing that, 2 kilograms. We're seeing a difference between drug and placebo over the course of a trial of maybe a pound or two, you know? It's not nothing, but it's not as big as what you're seeing with a drug like olanzapine.

But all the drugs will have all the data that we have access to, organized in the same way in the Warnings and Precautions section so that a clinician,

in selecting a drug, can go there and look to see what the effects we're seeing are on glucose, on lipids, and on weight. And it's broken down by mean changes, outliers, looking at patients who move from being abnormal at baseline to more abnormal, and by dose.

So it's broken out in a very detailed way and in the same format for every drug. It's the best -- we don't have head-to-head data, but it comes close.

DR. MURPHY: I think, Tom, that, first of all, I'd like to say I don't know why the final slide didn't have on it that FDA is and will be reviewing additional data regarding the metabolic AEs related to the use of these products. I mean, somehow that didn't make it on the last slide. It was supposed to.

And secondly, I think one of the issues that bothers the committee is we've done this now a couple of times with Abilify, these products, and we always see something like -- we always have these outliers. I mean, what you call the outliers, and they are always confounded, and we never have enough information about what other drugs they might be on.

But I think that what the committee is hearing is

that the division is well aware of this, and they are trying to get enough data that they can come up with some metrics and put it in the label in a way that makes sense to somebody who is prescribing it. So --

DR. LAUGHREN: That's probably more directly to the question. What we're looking at in this slide are adverse event reports, very difficult to make any sense of at all. And for a common background event like weight gain, we're not going to rely on spontaneous reports. We have much better data.

I think the question that was being asked is when we do have better data in a published report, can that somehow find its way into the label? And that's a very good question. We like to be able to look at the raw data. And in those instances where we can actually get the raw data, we are willing to consider putting that information into a label.

But what we have in detail are the data that the sponsors provide to us. It's difficult for us to get access to raw datasets. And as you well know, when you look at a published study, it's sometimes a pale reflection of what happened in a trial. So --

DR. ROSENTHAL: Okay. So we've got Drs. Mink and Chappell are the next two, and then there are some others beyond that.

DR. MINK: Just a question following up then. I understand that the Adverse Event Reporting System is not without its flaws, but as a practicing clinician who sees a number of children who are on this, the weight gain can be astounding in some of these children.

What I'm wondering in particular, given the data we heard about the relatively rapid onset of diagnosed diabetes mellitus plus the concern about weight gain, in the labeling for Abilify, the patient counseling information makes no mention whatsoever of weight gain, metabolic concerns. And I'm wondering if, at the very least, that could be added to the label to alert prescribers and to put in the patient counseling information that this is something.

It lists cognitive effects and motor performance. I would think that this is something that also would warrant mention at least that it's a potential concern.

DR. LAUGHREN: That's a fair point. I mean, the

Highlights section of labeling does very prominently label metabolic effects. And it will. I mean, let me read to you from sort of a template for the way it's going to look for Abilify when we finalize this in a few weeks.

So Invega has a section in Highlights called Metabolic Changes, and it's broken down into hyperglycemia and diabetes, dyslipidemia, and weight gain. And in the Highlights, it says for hyperglycemia, it says, "Monitor patients for symptoms of hyperglycemia and monitor glucose regularly in patients with diabetes or at risk for diabetes." That's for glucose.

For weight -- and this is true of all the atypicals. All the atypicals have the same language that you should be monitoring weight, you know, both baseline and periodically throughout treatment. But we'll look at the Patient Counseling section in the med guide and see if there's not something more we can do to add that information.

But I think, and I think you're seeing that from the differential prescribing that's going on, that

clinicians are aware of this, and they're even selecting drugs based on what their concern is about a particular patient gaining weight at baseline.

DR. ROSENTHAL: Dr. Chappell?

DR. CHAPPELL: I'm not a clinician. So I only had the report to go on, and I was somewhat at a loss because when I read it and I screened it, I had not much worry about a couple of pounds difference. I certainly wouldn't mind a child of mine being a couple of pounds heavier if he got a treatment that helped him.

On the other hand, a couple of pounds per month continually over years, that's a big problem. And I have no way -- because these are short-term results, I have no way of distinguishing them. So, as I often do with the FDA, I ask we don't know yet. How about longer-term studies?

And so, when we were told that we would have more information on BMI and weight, what do you mean by "more?" Bigger sample size, longer-term follow-up, both?

DR. MCMAHON: Well, I think I might have been the

one to mention that. I don't know yet exactly what the study or studies will look like. So I can't really say in any specifics because it's not yet even confirmed.

But the suggestion, what we're trying to do is to get -- at least to get baseline weights as part of a study, which would be claims based. That's what we're trying to accomplish. As far as how long the observation period, all that, it hasn't been fleshed out at all.

DR. CHAPPELL: That seems like it would help --

DR. LAUGHREN: What we do provide in the label for all the atypicals, and we'll be doing the same thing for aripiprazole, is to provide the data we're seeing in the long-term uncontrolled follow-up. We'll always have a cohort of patients who are followed up without a control group for 6 months or a year, and those children have their weights monitored. And so, we'll present those changes and then compare it to the normal curve and report it in terms of a percentile difference how far a change is from the norm, where it was at baseline and where it was.

The problem is that it's a changing cohort,

obviously, over time. You're losing patients along the way, and so it's hard to make too much sense of that. But it's the best that we have. It would be ideal, I agree, to have long-term controlled data. You know, again, you're not going to get that with a placebo. You might be able to get it with a head-to-head comparison across drugs.

DR. ROSENTHAL: Drs. Towbin and Wagener.

DR. TOWBIN: Well, I appreciate you gentlemen being here this afternoon. I know how hard you've worked to think about these issues carefully.

We've talked about the application of these drugs for off-label uses -- ADHD, irritability outside of autism, and so on. Another way in which we're seeing some off-label use is outside of the age range. And I was impressed with the use data that suggested there were, what, 19,000 prescriptions written for children who were between, what, 0 and 6 or 3 to 6 years of age.

It's possible that 1 percent of that represents a group with autism spectrum disorders. That would rival the prevalence of autism in the general population. But since we really don't have data on children in that

age range, one of the concerns I had is that this may, in fact, be an application for the drug being used for irritability in that age group in a nonspecific way.

I know we're not here to regulate practice, but I was wondering whether there would be room in a label to underscore that the safety and effectiveness of this drug had not been established in that age range?

DR. LAUGHREN: It does say that it hasn't been looked at below 6. I'm sure that it says that somewhere in the label. Because you're right. We don't have -- doesn't it say that, Mitch?

DR. MITCHELL MATHIS: Yes.

DR. LAUGHREN: We always say where we have data and where we don't have data, but we don't tell clinicians that they can't use it in that population. But we do tell clinicians where we have data.

DR. TOWBIN: I was looking more in the Pediatric Use section. And so, it may be elsewhere, but I was wondering if we could make it somewhat more prominent in the Pediatric Use section?

DR. MURPHY: I mean, Tom, there are some products where we do say explicitly that this has not been

studied for this condition in this population, and I think that's what's being asked.

DR. LAUGHREN: Well, we could certainly -- and we can fix this easily, saying what age groups in which it has been studied. We don't typically list all of the conditions in which a drug has not been studied.

DR. TOWBIN: This wasn't about conditions, but just to say that we really don't --

DR. LAUGHREN: Yes. Right.

DR. TOWBIN: -- have data on that age group.

DR. ROSENTHAL: Okay. So that's good. So you'll take that into consideration.

Dr. Wagener, you're up next.

DR. WAGENER: So I have two sort of brief things. First of all, I want to go back to the diabetes issue and what we first saw, relatively rapid onset. If you look at the patient insert, basically, it says that there should be under Warnings and Contraindications, "monitor glucose regularly in patients with or at risk for diabetes."

Would you say a 10-year-old is at risk for diabetes? That was just a question to the FDA.

Because if you don't think a 10-year-old is at risk for it, and yet we just saw data here that within 60 days they have a chance of developing it, then I would say you should get rid of that "at risk for" and just say "it should be monitored."

DR. LAUGHREN: So you're thinking that all use of an atypical in children should be accompanied by regular monitoring of glucose? I'm just asking.

DR. WAGENER: I think that you need to do -- I think there needs to be some way to alert an individual. The average pediatrician I do not think in reading the warnings here would sit there and think that their patients are at risk because they would say my typical 10-year-old is not at significant risk for diabetes.

DR. LAUGHREN: Well, again, going back to the figure that was reported in Dr. Gerhard's study, it was 5 per 1,000 patient-years --

DR. WAGENER: Right.

DR. LAUGHREN: -- in this age group. Again, I would like to know how that compares with the background rate.

DR. WAGENER: I agree with you. I completely agree with you, and that's totally -- it's largely dependent on how long patients were followed, et cetera, to determine the number of years exposure risk. We just have two pieces of data. That one, and when you looked at age of the very short-term use and the time to development was relatively short, which is an uncommon thing in a randomly selected population.

DR. LAUGHREN: I mean, I think pediatricians --

DR. WAGENER: So I'm not disagreeing with your data there. What I'm challenging you on is somehow to raise alertness to a group of patients that you may be putting at risk by starting on this drug, specifically the risk of diabetes.

DR. LAUGHREN: Right.

DR. WAGENER: The second thing I wanted to just mention, and this is an anecdote. So it's totally worthless. But within my practice, the use of Abilify has -- as an inpatient hospitalist, the use of Abilify seems to be increasing. Under the use data that I have here, I have no way to know that. I simply know that it's being used at a certain number of doses in the

last few years. And so, trending would be helpful.

We heard a comment here that suggested that it's plateaued in its use. What the anecdote is, is that where the psychiatrist used to be the person prescribing this drug, the general pediatrician is more frequently doing that now.

Again, the psychiatrist may be very focused on and experienced with these five different medications and knows some variable things, where the pediatrician might not. So I'm looking at how do you put within the label some of these advices to them to be aware of potential side effects?

DR. LAUGHREN: I want to come back to the issue of doing routine monitoring for glucose for every patient who is prescribed an atypical antipsychotic. Maybe that is a good idea. Maybe it is not. But it surely changes the practice of medicine to do that.

DR. WAGENER: I believe I said routine monitoring for diabetes. That doesn't mean doing blood glucoses necessarily. That means being aware to watch the patient and maybe even counsel the patient in watching for polyuria, polydipsea, something --

DR. LAUGHREN: It says that now. It says monitor for symptoms of diabetes if you're using this drug. Do that in everybody. But it doesn't say routinely monitor glucose. It does for olanzapine, the worst actor in this class. But up to now at least, we haven't. But they all say monitor for emergent symptoms of diabetes, and it lists all those things that you mention.

DR. ROSENTHAL: All right. Dr. D'Angio?

DR. D'ANGIO: I wanted to go back to the issue of weight gain, and I agree that controlled clinical trials have their advantages in many ways in being able to compare subjects to subjects who are on placebo and getting some idea of weight gain over time that way.

The disadvantages of clinical trials have also been pointed out many times to us today in terms of the fact that the selection for subjects who are potentially least likely to have side effects, relatively short periods of follow-up.

And I think that we potentially, to our detriment, put aside the impressions of clinicians of weight gain that is significantly more than "a couple pounds a

year" and put aside the reports of extreme weight gain that we've seen in some of the other monitoring that FDA has done. I think it would be a mistake to leave the impression that FDA is minimizing the metabolic effects of these drugs.

DR. ROSENTHAL: All right. And Dr. Taylor, can you put up the question while Dr. Kocis asks the last short question?

DR. KOCIS: It will be quick. My only comment was back to the label and Section 8.4 as it currently exists, and I'm thrilled to hear that new labeling will be out shortly. My only question is will it follow the new guideline for labeling?

Going back to Section 6.2 and trying to tease through all the different pediatric adverse events, while they're there, they're difficult to find, difficult to read through, difficult to interpret. And obviously, the new label guidelines were put in place to ease that, to help clinicians understand. And so, that's the question.

DR. LAUGHREN: Okay. Again, the Abilify label with regard to metabolic effects will look very much

like Invega. If you want to go look at Invega, paliperidone, and it will all be in Warnings and Precautions, all laid out. First, hyperglycemia, then lipid changes, and then weight changes, broken out adult, pediatric. Broken out by dose, looking at mean changes, looking at outlier analyses, looking at patients who are actually slightly abnormal at baseline and how much they change on drug.

So it's all going to be in the same format for all of these drugs to make it easy for clinicians to find that information.

DR. KOCIS: So, to be clear, Section 8.4 will be populated with all the data that's spread all over in 6.2, concise and --

DR. LAUGHREN: It's all going to be in Warnings and Precautions.

DR. KOCIS: 8.4?

DR. LAUGHREN: No. No --

DR. MURPHY: He's asking if --

DR. LAUGHREN: No, no, no. It's going to be in -- Warnings and Precautions is 5, right? Well, 6 is Adverse Reactions. 5 is Warnings and Precautions. So

it will be in Warnings and Precautions.

But it's mentioned in the Highlights, the first half page. And so, clinicians are directed to that section where they can find the full details.

DR. ROSENTHAL: All right --

DR. MURPHY: I think -- let me just make -- I think what Dr. Kocis was trying to get at is, is there anything specific to pediatrics that's going to go in the Pediatric section or refer them in the Pediatric section that is back in Precautions that is specific to pediatrics?

DR. LAUGHREN: You know, we can easily put a reference back to Warnings and Precautions from Pediatric Use if we haven't already. We're not going to repeat it in Pediatric Use.

DR. MURPHY: If there's anything specific just to pediatrics, it will be spelled out in the Warnings and Precautions. And then you'll say in the Pediatric section, see the whatever number it ends up being in Precautions that's about pediatrics?

DR. LAUGHREN: Yes. Well, we can certainly do that.

DR. KOCIS: And again, just to be clear, it's going to be completely different than 8.4 is in the current label?

DR. LAUGHREN: Well, 8.4 is probably not going to -- but it will include a reference back to where a prescriber can find the complete metabolic information.

DR. KOCIS: That's my point. If you go back to 6.2 in here and you try to tease through and make sense, we've read this, we've reviewed this, we know this. And I'm still having difficulty going through 6.2, trying to tease out the peds data and then try to make sense of am I going to do glucose monitoring of A1Cs or what not?

And I thought the whole intent of the new labeling guidelines were to put all of that information one-stop shopping, not that you're bouncing all over the label to make clinicians who may be knowledgeable, but not thoroughly knowledgeable have an easy, direct access to the current information.

DR. LAUGHREN: What we try and do in the current approach to labeling in the Highlights section is tell clinicians all the things, all the actions, all the

monitoring that we're recommending. So it says that with regard to metabolic, it says monitor weight in everybody. It says look for symptoms of emerging diabetes in everybody and monitor glucose in patients who have a risk of becoming diabetic or who have diabetes, obviously.

So, any monitoring we try and highlight in the very first Highlights section. And it's repeated then in Warnings and Precautions, and we'll put a reference from Pediatric Use back to the section in Warnings and Precautions where a prescriber can find the detailed information.

DR. ROSENTHAL: I think you've agreed to what the committee has been asking for, which is that you -- that with this upcoming revision of the label, that you carefully consider the language around pediatric use and adverse events related to this medication.

DR. LAUGHREN: But if I could just briefly come back to this issue of these cases of these reports of huge weight gain over a period of 6 months or a year, these are very, very difficult to interpret with regard to causality. And again, all you have to do is read

the newspapers about the alarm about obesity in kids. And I mean, I hear stories about this all the time.

My kids were in high school a couple of years ago, and I used to go to some of the football games, and you look at these 14-, 15-year-old boys who weigh 300 pounds. And this is when they're in football season when they're training every day. You hate to see what would happen when football season is over.

I think it's very important to keep these things in context. I don't know what the value is, when we have systematic data, of describing these handful of cases of huge weight gain. I don't know what it means.

DR. MURPHY: I think, Tom, what it means to people is that if you have a clinic or an office, and you're seeing a lot of patients and you're putting some of these patients or you're taking care of patients who are on this. And most of them don't do this, and you do have these extreme weight gains, you can look at all the other things. You simply are going to say I have these other patients on this product -- let's say a different one of the antipsychotics -- that may or may not be seeing the same extreme weight gain. So if you

see extreme weight gain.

Because these are people who are seeing kids all day every day. So they have an idea of what the background rate is, I think is what they're saying to you. And the reason we do studies is because we can't rely upon our own sample, if you will.

But I think they're just saying that we -- they're not asking you to put this as a fact in the label. They're saying we're concerned about it, and we think it needs to be studied. And we're looking at the data that came out of Rutgers, and we think that that has concerning elements to it because that's diabetes. That's not even weight.

DR. ROSENTHAL: Yes. Dr. McMahon?

DR. MCMAHON: Hi. I know we need to move on, but I just want to say that -- reiterate something that I said this morning about AERS, which is that it is difficult in a high background situation to make a lot necessarily out of case-by-case in AERS and that it's really most useful for less high background events.

And I don't think that means we should ignore it, but I think that if we have other data sources that are

a little bit more enlightening, then we might want to turn to those in those situations more, a little bit more so.

DR. ROSENTHAL: Thank you.

Okay. Well, let's go ahead with the voting question. Dr. Wagener?

DR. WAGENER: Just to reply to that, in the package insert, there is a comment. Two short-term placebo-controlled trials in children. Most of the data showing very little difference in weight as adult data, a huge amount of adult data showing very little difference.

But here in your insert points out that the average weight gain with the therapy group was 1.6 kilograms versus 0.4. No statistics are given. Proportion of patients meeting a weight gain criteria greater than or equal to 7 percent of body weight, 26 percent in the treated group versus 7 percent in placebo. No statistics given.

I don't know whether that's statistically significant or not. But if I looked at that in combination with the AERS, I'd be worried that in

children, weight gain is a bigger problem than in adults.

DR. LAUGHREN: What you're quoting are the data from the autism studies. We didn't see that in the schizophrenia or the bipolar studies. In the autism studies, there was no difference in mean change from baseline. The only difference was this difference that was reported.

And this will -- this will all be moved up to Warnings and Precautions. What to do, what to make of that, it's hard to know. I'm open to suggestions about how to interpret that. Again, we're not seeing that sort of signal in the other pediatric disorders that have been studied. It's only seen in these two studies in kids with autism.

I don't know what it means, but we report it.

DR. ROSENTHAL: So I think the agency is probably better positioned than we are on this committee right now to completely resolve this question of the exact wording in the label. But I think the committee -- I'm speaking for the committee when I say that there is a general appreciation for the fact that the agency is

going to look at the label and try and make sure that it's very clear around these issues as they pertain to pediatric age group.

All right. So we have each learned from our various orientations that routine monitoring is all but routine. It's an active process. So the FDA is recommending continuing routine ongoing post-marketing safety monitoring for aripiprazole. And the question to the Pediatric Advisory Committee is do members concur with that recommendation?

So we'll take a vote first by raising of the hands, and then we'll go around the table and people can state their votes into the -- Dr. D'Angio?

DR. D'ANGIO: Can I just ask a clarifying question?

DR. ROSENTHAL: Yes.

DR. D'ANGIO: That is assuming that the FDA is also going to be working on the label, that the studies of weight gain that Dr. McMahon has talked about are being planned. Is that correct?

DR. ROSENTHAL: So I think --

DR. MURPHY: We are planning them. Okay?

DR. D'ANGIO: They're being planned, which is good.

DR. MURPHY: But I guess they haven't been awarded or -- you know what I'm saying? So we're telling you we're trying, but we don't have always control over the very last, final part of all this.

DR. D'ANGIO: This is the question that comes up every time we had an active discussion and we're asked to answer a question that was asked before the discussion. Should we assume that what you said, that the rest of the actions that were discussed are underway and that we don't have -- that voting for this doesn't mean that we're voting against you doing what you said you were going to do?

DR. MURPHY: Absolutely. It doesn't mean that.

DR. D'ANGIO: Thank you.

DR. MURPHY: It means that you're voting for this, and you can say it and Geoff can say it that way so it shows up in the minutes. And remember we showed you up on the Web, you can go see, just like it said before. You were unhappy with this label, okay? So it can say you're voting to return to routine monitoring based on

the following actions. I mean, you can say that.

DR. ROSENTHAL: Okay.

(Laughter.)

DR. ROSENTHAL: Well, so does the agency feel it's important for us to specify, re-specify these actions, or was the discussion that we've had for the last hour sufficient?

DR. MURPHY: I think the committee thinks it's important. That's what I'm hearing.

DR. ROSENTHAL: That was the next question I was going to ask.

DR. MURPHY: I think the committee wants us to say -- I'll try, and Tom, you agree or disagree with me. I think right now that the FDA recommends continued routine ongoing post-marketing safety monitoring, that we go to that in view of the fact that the agency is planning to change the Abilify label to reflect more accurately we think, due to the additional information, the metabolic effects in pediatrics.

And we also are going to continue to try to better ascertain what's going on with weight. We're just not telling you we're going to be able to deliver the

results, but we're definitely going to try.

So those are the two caveats that I'd say that you're putting on this recommendation.

DR. ROSENTHAL: Dr. Towbin, are you going to clarify the question?

DR. TOWBIN: Well, perhaps. I'm curious about what the implications would be if we did not concur. What would be the actions that would follow?

DR. MURPHY: You could ask us to come back in a certain period of time and give you the follow-up. You could ask for another safety review of AERS. You could ask that you want another update on the AHRQ, Dr. Gerhard's report. You could ask, you know, a lot of things.

DR. LAUGHREN: Okay. I want to -- before we go to the vote, I want to clarify, Dianne, what you said about looking at weight. Were you suggesting that there was going to be some study looking at weight or --

DR. ROSENTHAL: Please speak into the mike, Dr. Murphy.

DR. MURPHY: I think we're saying that we are

trying to have put together a study that would be looked at using baseline weights, where you have baseline weights.

DR. LAUGHREN: Well, but I don't think that's what's being suggested. I think there's an interest in knowing what actually happens to weight as an outcome over time, not whether or not baseline metabolic status and weight can be recorded and used as an adjustment in a cohort study looking at Type 2 diabetes.

I mean, I thought that's what was on the table, but --

DR. MCMAHON: Well, I think my sense is that both of those things would be of interest, right?

DR. LAUGHREN: But can you get weight as an outcome in a claims study? I mean, I don't --

DR. MCMAHON: Well, we're trying. I don't know if it's going to happen or not.

DR. ROSENTHAL: Okay. So now I'm going to reframe this question. And Dr. D'Angio, I might ask for you to help me when it comes time.

So the current question that the committee is willing to vote on, I believe, is the question of does

the committee concur with an FDA recommendation to continue routine ongoing post-marketing safety monitoring with the following two caveats, that the agency will work with the sponsor around clarifying language in the label pertaining to pediatrics, metabolic effects, and weight and -- Dr. D'Angio?

DR. D'ANGIO: And that the FDA continue to attempt to address -- attempt to gather further data concerning weight gain and metabolic effects in pediatrics.

DR. ROSENTHAL: Okay. That seems like a clear question to me.

DR. D'ANGIO: Although I think there are some people who might still vote against that down at that end of the table because they want -- they would like the FDA to come back to us.

DR. ROSENTHAL: That -- well, okay. I'll take up that issue as a second vote, okay? But let's vote on the first thing first. So does everybody understand the question that we're voting on? Okay.

So all in favor of that proposition?

(Show of hands.)

DR. ROSENTHAL: All right. Any opposed?

(Show of hands.)

DR. ROSENTHAL: Any abstentions?

(No response.)

DR. ROSENTHAL: There was one opposed, no abstentions. Let's go around the table. So, Dr. Vaida, if you can please state your name and then your vote. And if you'd like, you can give a brief statement about why you voted the way that you did.

DR. VAIDA: Allen Vaida, and I voted for approval of what was put on the table. And I think we've pretty well explained it. I don't need to add anything more.

MS. CELENTO: Amy Celento. I voted yes. But I also want to mention there was earlier discussion about indicating on the label that the Abilify has not been shown to be safe or effective in children under 6, and that wasn't mentioned. But I think you got that. So, thank you.

DR. D'ANGIO: Carl D'Angio. I voted yes, and I voted yes because I agreed with what Geoff and I put together and because we will be addressing the issue of when the FDA should come back to us.

MS. EICHNER: Marilyn Eichner. I voted yes for

what was presented on the table.

DR. BALIS: Frank Balis. I also voted yes. There certainly were enough questions that came up with this discussion to indicate that monitoring should continue.

DR. REED: Michael Reed. I voted yes. I think, as was just mentioned, there is enough that we need to continue to monitor, and I'm just hoping that what our discussion -- the central theme of our discussion that came out today is going to be embedded into that revised label because I think by the time we get additional data, you think of the lag time it's going to take to revise yet again another label.

And I may be a little dense, but it just sounded to me that the label changes was coming more of intent that if you have diabetes or you believe you're at high risk of it versus a drug-induced effect.

DR. CHAPPELL: Rick Chappell. I voted yes, and much of what I was going to say was said more ably just now by Dr. Reed. But also even though I didn't want to wait for the labeling adjustment for more data, I want to reiterate my request, my emphasis on the importance of longer-term data to see how big of a problem these

weight gains really are.

DR. ROMERO: Jose Romero. I voted yes I think for all the reasons that have already been stated in the discussion and by the members prior to my vote.

DR. WAGENER: Jeff Wagener. I voted no because I don't see how the FDA has responded to the December 8, 2009, request by this committee in a thorough fashion, and I feel that if it's taken them 2 years not to respond to that, that we need to be more in an observational role.

DR. MINK: John Mink. I voted yes, mostly in light of the promise that we will have another, second vote on a separate question. I do think, as has been discussed, there is serious concern that there may be -- the children may be at higher risk for more serious adverse events, and we just don't have sufficient data to answer that question.

DR. TOWBIN: Kenneth Towbin. I voted to concur. I do think the monitoring plan is a reasonable plan. I think we just want to hear more about this going forward.

DR. DURE: Leon Dure. I voted yes because the

question is, is to continue with monitoring. I do think, though, that there's been more discussion about this issue related to the atypicals over the years. There probably needs to be a discussion. It doesn't have to be adversarial, but one that's separate from our usual approvals meetings. Because we do totally bog down when we -- whenever we touch an atypical antipsychotic.

DR. RAKOWSKY: Alex Rakowsky. I voted yes for the reasons we already discussed.

DR. BRINKER: Jeff Brinker. I voted yes.

DR. WHITE: Michael White -- there we go. I voted yes. I'm very concerned about the incidence of diabetes, but I'm not sure that weight is the best parameter to use for a measurement, and I think a carefully designed study to investigate metabolic effects is in order.

DR. MOTIL: Kathleen Motil. I voted yes for the discussions that have been already presented.

DR. KOCIS: Keith Kocis. Yes. And I don't like the word "routine," but it's a 2-year ongoing discussion and trying to gather more facts that should

continue.

DR. ROSENTHAL: All right. So let's circle back to this other issue of when the committee would like to circle back with the agency.

First, I'd like to just solicit some input from the left side of the -- my left side of the table. What do you guys think would be reasonable in terms of timeframe to circle back again and assess this, or do you think there's a different forum in which we should explore these potential associations between atypicals and these metabolic factors in pediatrics?

Any ideas?

DR. MITCHELL MATHIS: Mitchell Mathis. I'm a deputy director in psychiatry.

I think the first part of your question was when can we accomplish these labeling changes?

DR. ROSENTHAL: Well, no, I think the committee would -- what I was hearing, what I was hearing is that I think people would like to discuss these issues again, perhaps even in a different forum, to more -- to have less encumbered discussions of metabolic effects in the pediatric age group, although I'm maybe making

that up. Is that what people were thinking?

Next question would be if we were going to circle back in the context of the Pediatric Advisory Committee to assess the work that's been done that's been discussed today, what would be a reasonable timeframe for that revisit? Would it be a year from now? Would it be 2 years, 6 months? What are your thoughts?

We want to give you enough time to accomplish the goals that we've laid out.

DR. MITCHELL MATHIS: Well, I can't speak for when the study that we're attempting to do might get going and get done. But we will have these labeling changes where we specifically identify what happens metabolically to children very clearly in the label done by this fall. It requires some back-and-forth with the sponsor. We can't predict exactly, but we will get it done very soon.

DR. LAUGHREN: The only study that I heard talked about was a next version of the retrospective cohort study perhaps with some better metabolic data at baseline to use in making adjustments, but still looking at diabetes as the endpoint.

But I can't speak to that because I don't really have that much to do with that study. I'm not aware of any other study that we're talking about being done here.

DR. MCMAHON: Okay. So, I mean, I don't feel comfortable being very specific about a study that hasn't yet come to pass, you know? I mean that hasn't really been completely designed.

So, I mean, we would hope to have parameters, look both at diabetes, but also at weight if possible as an outcome as well as a baseline.

DR. ROSENTHAL: So may I ask for an update to the Pediatric Advisory Committee within a year of progress on this?

DR. MURPHY: I think that would be too short, Geoff. I really do.

DR. ROSENTHAL: Okay.

DR. MURPHY: Because I think -- I think, first of all, I'd like to say I know it's been 2009 that the committee asked this last time. But it's not like we haven't been doing anything. We convened an entire group at NIH to try to work out how to answer some of

these questions, and they reported back to this committee that they didn't have any really good answers, okay? So we did that first.

The next thing we did was what you just heard. So I guess the question is, well, why didn't we change the label in the meantime? I think where the committee is now in 2011 is we want you to change the label while you're looking for more data. I mean, that's the way I'm interpreting what's happening, and I think the division said they're going to do that.

DR. ROSENTHAL: Yes.

DR. MURPHY: And so, that means that for us to come back to you again, we really ought to have more data.

DR. ROSENTHAL: So let me clarify about what I was thinking we would get an update about. I was thinking that we would see the new label, which is only supposed to take a few months, and we would just --

DR. MURPHY: We will send that to you. We could send that to you, no problem.

DR. ROSENTHAL: And that we would just hear -- we would just hear from you how these ideas about next

studies are crystallizing in the minds of the people who are considering the best designs and ways to obtain these data. I'm not -- I didn't pick a year thinking that we would have the outcome from studies, just that we would get an update on the process, I think.

DR. MURPHY: We don't mind giving an update at all, as long as the expectations aren't that we're going to be able to deliver something we know we can't deliver. That's all we're trying to prevent are expectations that we can't deliver on.

DR. ROSENTHAL: And what I just described, does that seem reasonable? I'm not trying to create unreasonable expectations here.

DR. MURPHY: No. We will mail you the label as soon as we get it, the changes. And we'll plan to have a meeting within a year, year and a half, because we're already doing a year out, and it's not on that.

DR. ROSENTHAL: Yes. Okay. Okay.

DR. MURPHY: For an update as to where we are within our saga of trying to get better data on the problems of this metabolic issue in antipsychotics and children. I mean, you want to assurance I think is

that you're going to know how we're progressing or not progressing, and we will do that within a year to a year and a half. As long as I'm here.

(Laughter.)

DR. ROSENTHAL: God willing. Well, okay, we've got -- well, Dr. Brinker and then Dr. Dure. And if you gentlemen can please make your comments as succinct as possible, that would be great. We're already -- we've spoken through our break and into the next session.

DR. BRINKER: Well, something very quick from a relatively ignorant person. You can look for things like this in big population studies or you can have focused studies to try to figure out an impugned pathophysiology for either weight gain or diabetes. And I was wondering if an appropriate young animal study which was given a carbohydrate diet might help elucidate whether that is an issue, as opposed to older animals which might act more like adults?

DR. MURPHY: That's a good question, and we can take it back to our juvenile animal model people and see because, as you know, there are different models that are good for different things. So that is

something we will bring back to them.

DR. ROSENTHAL: And Dr. Dure would like to make the last point before we take a break.

DR. DURE: This is really brief. Just if you have a meeting, I can't imagine having a meeting with data in a year and a half, but there is this tension between what we as pediatrics folks see as risks and how serious they are and what tends to show up in the label. And I really think that it may be time for a real discussion about that because we may need to be recalibrated, and that's it. Really, we just need to have that discussion.

DR. ROSENTHAL: Thank you.

We'll take a 10-minute break. Thank you all for this robust conversation, and we'll see you in 10 minutes to start talking about Afluria and the influenza vaccines.

I'd like to remind committee members to please not discuss the topics at hand during the break.

(Break.)

DR. ROSENTHAL: Let's sit down and get started again. If people can start finding their ways to their

seats?

All right. A number of people have called me on a process point, which is legitimate. Before we voted at the end of the last session, I promised that we would have a second vote on whether or not we would like the agency to circle back with us at some point.

My feeling was that we resolved that point in the discussion that followed the first vote, but we should probably vote on that as well because my understanding isn't necessarily reflective of the group.

So I think what we talked about -- and we're not actually going to be able to discuss this very much because those from the agency who were participating in this discussion have left. But let me just paraphrase what I think -- what I'm remembering what I think we all agreed to.

I think we said that we would like to see the new label, and so -- and I think what we can do is in 12 to 18 months or so get an update from the agency as to progress that's being made in terms of thinking about studies or designing studies or identifying partners for studies that can help us address some of these

metabolic issues in pediatrics.

So that's my understanding of where we were. And so, why don't we just formulate the second vote around those two points? One is that we will receive the label, and then the second point is that we will circle back, the agency will circle back with the Pediatric Advisory Committee in 12 to 18 months for an update of those things I just mentioned.

All in favor of that, if you can please raise your hands?

(Show of hands.)

DR. ROSENTHAL: And is anyone opposed?

(No response.)

DR. ROSENTHAL: Okay. Let's just quickly go around the table. Dr. Kocis, will you get us started this time?

DR. KOCIS: Yes.

DR. MOTIL: Oh, it's me. Kathleen Motil. Yes.

DR. WHITE: Michael White. Yes.

DR. BRINKER: Jeff Brinker. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. DURE: Leon Dure. Yes.

DR. TOWBIN: Kenneth Towbin. Yes. Thank you.

DR. MINK: John Mink. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. ROMERO: Jose Romero. Yes.

DR. CHAPPELL: Rick Chappell. Yes.

DR. REED: Michael Reed. Yes.

DR. BALIS: Frank Balis. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. D'ANGIO: Carl D'Angio. Yes.

MS. CELENTO: Amy Celento. Yes.

DR. VAIDA: Allen Vaida. Yes.

DR. ROSENTHAL: Okay. Thank you very much.

All right. Now I think we have some team members from the FDA who may be joining us by teleconference for this next session. Is that -- Walt, do you know? Is that true?

DR. ELLENBERG: We're expecting one individual to call in. I have not heard -- we're online live right now. The individual has not called in.

DR. ROSENTHAL: And is Dr. Nolletti ready?

DR. NOLLETTI: Hello. My name is Dr. Cynthia Nolletti, and I will be presenting the pre-licensure

safety data for Afluria this afternoon.

Afluria is a trivalent, inactivated, split virion influenza vaccine manufactured in eggs. In November 2009, approval was granted to Afluria for the active immunization of persons 6 months and older against influenza disease caused by influenza subtypes A and type B present in the vaccine.

For reasons that will become clear during Dr. Nguyen's presentation, in July 2011, the indication and usage of Afluria was changed to the active immunization of persons 5 years and older. But I will be presenting the pre-licensure data that was the basis for the November 2009 approval, which is the trigger for today's PAC.

Each 0.5 milliliter dosage contains a total of 45 micrograms of influenza hemagglutinin antigen, 15 micrograms of each of the three strains that are recommended for the current season -- H1N1, H3N2, and B strain. Afluria is unadjuvanted.

Afluria is supplied in 0.25 milliliter and 0.5 milliliter prefilled single-dose syringes that are preservative free. The dosage of Afluria for children

6 months to less than 3 years of age is 0.25 mLs and for children 3 years and older is 0.5 mLs.

Children 6 months to less than 9 years of age receive 1 or 2 doses administered intramuscularly 4 weeks apart, depending on their vaccination history. And children 9 years and older receive a single dose intramuscularly.

I'm going to move on to the regulatory history now. In September 2007, accelerated approval was granted to Afluria for use in adults 18 years of age and older. The original BLA included data from a small, uncontrolled, non-IND pediatric study of 298 children. The study was submitted only to support safety.

In July 2009, CBER asked CSL to consider resubmitting the original pediatric data as a new supplement to support accelerated approval of Afluria for use in children. This request was precipitated by the 2009 H1N1 pandemic, during which time there was an urgent need to expand the supply of vaccine for use in children 6 months and older. So, on November 10, 2009, accelerated approval was granted in children 6 months

to less than 18 years of age.

I'm going to present the pre-licensure data now. This first slide summarizes the pre-licensure safety data in adults. The original BLA contained 1 pivotal and 4 supporting studies in which a total of 1,741 adults received CSL influenza vaccine.

There were no deaths or serious adverse events among these studies, and the table presents the most common adverse events in the pivotal Phase III study. The table is divided into the two treatment groups, Afluria on the left and the placebo group here in the right.

First are listed the solicited AEs that occurred at a rate of 10 percent or more, the most common solicited SAEs. Most common was injection site tenderness, 59.8 percent, and second, injection site pain, 39.8 percent, both of which occurred much more frequently than in the placebo group. The other common solicited AEs included headache, malaise, and myalgia, and these occurred at frequencies closer to those observed in the placebo group.

Among all the reported unsolicited AEs, there was

only one that occurred at a rate of greater than or equal to 5 percent, and that was headache. This occurred in 7.5 percent of adults, not much more frequently than in the placebo group, 5.6 percent.

So we concluded from the pre-licensure safety data in adults that there were no unusual trends or safety concerns.

Moving on now to the pre-licensure safety data in the pediatric study. Again, this study consisted of or was conducted in 298 influenza vaccine naïve children 6 months to less than 9 years of age. The study was divided into 2 age cohorts, Cohort A, children 6 months to less than 3 years, all of whom received a dose -- 2 doses of 0.25 milliliters intramuscularly 30 days apart, and Cohort B, children 3 years to less than 9 years of age who received two 0.5 milliliter doses 30 days apart.

This study included a third dose that was administered 12 years following the first vaccination, and the company's rationale for this third dose was simply that this is the way influenza vaccines are administered annually. So they wanted to better

understand the safety and immunogenicity associated with annual vaccination.

The study was conducted at two sites in Australia in 2005.

Safety monitoring for the pediatric study consisted of solicited local and systemic events, recorded on diary cards for 7 days following each dose, unsolicited adverse events collected for 30 days after each dose, a follow-up visit 30 days after each dose, and serious adverse events collected 180 days, or 6 months, following each dose.

Serious adverse events are summarized on this slide. There were no deaths. There were a total of 21 SAEs throughout the entire study. Sixteen of the serious adverse events occurred 30 days post-vaccination and were assessed by the investigator as being unrelated.

Three SAEs occurred within 30 days of Dose 1 or Dose 2 and were also assessed as being unrelated to the vaccine. These included a case of diarrhea with dehydration and fall, picornavirus pneumonitis, and RSV bronchiolitis.

Two serious adverse events occurred within 30 days of the Year 2 dose, and both of these were assessed as being related. Both occurred on the evening of vaccination, and both involved fever and vomiting. One was associated with a febrile seizure.

The first subject was a 3-year-old female who developed a fever to 104 degrees Fahrenheit and vomiting on the evening of the Year 2 dose. She was hospitalized for hydration, had a throat swab that was negative for influenza, and fully recovered. The event was assessed as being possibly related to the vaccine by the investigator.

The second child was also a 3-year-old female who developed fever to 101.8 degrees Fahrenheit, also associated with vomiting on the evening of the Year 2 dose. This was associated with a febrile seizure that was described as lasting 10 seconds during which the child was unresponsive for 5 to 7 minutes.

The child was observed in the emergency room for 2 1/2 hours, was still febrile on discharge to 102 degrees Fahrenheit. However, she fully recovered. The event was assessed by the investigator as being

possibly related to the vaccine.

This next slide just lists the other SAEs following Dose 1 and Dose 2 through 6 months that were not assessed as being related. They occurred beyond 30 days after vaccination and included urinary tract infection, diabetes, asthma, meningococcal sepsis, autism, laceration, rotavirus.

This slide lists the SAEs that occurred after day 30 following the Year 2 dose and again assessed as being unrelated -- asthma, viral gastroenteritis, urinary tract infection, hypoglycemic seizure, tonsillectomy, viral pharyngitis, and mesenteric adenitis.

This next slide summarizes the solicited adverse events following all three doses. The most common local solicited adverse event was injection site pain, and the most common systemic adverse events were irritability, fever, rhinitis, cough, and loss of appetite.

The table presents the rates of these events according to the age cohorts and dose. Pain was the most common local event and occurred more frequently in

older children than in the younger age cohort. It occurred in 59.2 percent of the older children after Dose 1, 61.9 percent after Dose 2, as compared to 36.4 percent and 37.1 percent in the younger age group. In both age groups, the frequency of local pain increased following the Year 2 dose.

Systemic events solicited adverse events are listed here, and these occurred more frequently in the younger children as compared to the older children. Most common were irritability in the younger children following Doses 1 and 2, occurred at a rate of 47.7 percent and 41.1 percent, compared to 20.4 percent and 17 percent in the older children.

Rhinitis occurred in 37 to 47 percent of younger children, compared to 21 to 28 percent of older children. I'm going to discuss fever in more detail next. And then cough occurred in somewhat similar frequencies between the two treatment groups. Loss of appetite was also observed more frequently in younger children, 19 to 24 percent following Doses 1 and 2, and 7.5 to 5.4 percent after Dose 1 and 2 in the older age group.

There was no clear increase in the frequency of these events between Dose 1 and Dose 2, and again, pain and fever seemed to increase after the Year 2 dose.

Looking more closely at fever, which was defined as a temperature of 38 degrees centigrade or greater than or equal to 104 degrees Fahrenheit orally. Fever was more frequent in the younger children, group A, occurring after Doses 1 or 2 at a rate of 22.5 percent versus rates of 15.6 percent and 8.2 percent in group B.

There was an increase in the -- after the Year 2 dose to 39.5 percent in the younger children and 27.0 percent in the older children. The significance of this was not clear, given the small sample size and the absence of a control group.

This next slide summarizes the safety results for the pediatric study. Rates of fever in children 6 months to less than 3 years of age following Dose 1 or 2 was 22.5 percent. Rates in children 3 to less than 9 years of age ranged 8.2 to 15.6 percent following Dose 1 or Dose 2. The rates of fever were higher after the Year 2 dose, and again, the significance was not clear

in the absence of a control group.

There were no deaths in this study. There were two related serious adverse events, both fever and vomiting on the evening of the Year 2 dose, one of which was associated with a febrile seizure.

The febrile seizure rate in this study was 1 out of 298 subjects, for a rate of 0.3 percent, with 95 percent confidence intervals of negative 0.96 to 2.96. As a point of reference, the prevalence of febrile seizures in children is reported as 2 to 5 percent by the age of 5.

The significance of this rate again was not clear in the small study without a control group. With 95 percent confidence intervals that included zero, it could have been a safety signal, or it may have occurred by random chance alone. So, to summarize, there were no clear safety signals identified in review of the pediatric data.

Our conclusions, upon reviewing this data, were as follows. The 2009 H1N1 pandemic changed the risk-benefit considerations for pediatric licensure of Afluria. The data from the pediatric study was very

limited but suggested that Afluria was safe and immunogenic in children 6 months to less than 9 years of age.

Therefore, accelerated approval was granted with the sponsor's agreement to complete ongoing pediatric safety and immunogenicity studies, which they had agreed to conduct upon approval of the original BLA.

Are there any questions?

DR. ROSENTHAL: Before we go on to questions, I'd just like to make a note that our colleague Dr. Carl D'Angio has removed himself from the committee table and will not be participating in the discussions or the vote.

Yes, Dr. Dure?

DR. DURE: Just a clarifying question. Was the Year 2 dose split like the first year?

DR. NOLLETTI: It was just a single, it was one dose.

DR. DURE: Okay. So they had two doses the first year --

DR. NOLLETTI: So it was a third dose.

DR. DURE: -- and then just one the second year?

DR. NOLLETTI: Right.

DR. DURE: Okay.

DR. ROSENTHAL: Other questions? Anything else about Afluria? Were we going to vote on this?

DR. MURPHY: You have to do the safety review. This was the pre-licensure.

DR. ROSENTHAL: Oh, I see. Okay. Thank you for helping me stay oriented.

Has anyone called in on the line from the FDA? Okay.

All right. Well, next Dr. Nguyen will be presenting the standard review of adverse events for Afluria.

DR. MURPHY: Just so you won't feel bad, Geoff. We make it confusing. We give you two handouts, but one presentation per drug. And we give you one handout and two presentations per biologic. So that's --

DR. ROSENTHAL: I just thought Walt was shuffling my papers again.

DR. MURPHY: Please introduce yourself.

DR. NGUYEN: Hi. I'm Michael Nguyen.

Thank you to the committee for your service to the

nation.

I'll be talking today about the pediatric safety and utilization for Afluria. My talk is going to have three main objectives. I'm going to first talk about the background where I'll introduce the timeline for major regulatory actions and vaccine safety events. I'll talk about vaccine antigens, dose distribution, and label changes.

I'll then move on to do the actual adverse event review, where I'll talk about three different influenza seasons that are relevant to this adverse event review. The 2009 and 2010 Northern Hemisphere vaccine -- I know it's 5:00 p.m. So I will emphasize that the Northern Hemisphere is abbreviated "NH" from this point forward.

And I will also talk about the 2010 Southern Hemisphere vaccine season -- excuse me, influenza season, abbreviated "SH" from this point forward. This season is important because it had a signal. And then I will follow with the subsequent season, and then I will end the talk with the planned pharmacovigilance studies.

So, timeline. FDA approved Afluria for children 6

months to 17 years of age in November 2009. This is the trigger for the PAC review. Subsequently, in the next couple of months, during the Southern Hemisphere influenza season, Western Australia identified a febrile seizure safety issue with Fluvax, which is their version of Afluria. And because of this signal, they suspended their influenza vaccine program in children less than 5 years of age.

The next day, Australia followed and suspended their national influenza program for children less than 5 years of age. New Zealand followed quickly after that, 4 days later, and did the same.

Now in this setting, the U.S. was watching what was going on down in the Southern Hemisphere and decided to take action. It took a couple of months, but they realized that the signal was really only associated with a single vaccine, and it was not associated with the monovalent vaccines or the rest, the remainder of the trivalent vaccines.

So, in reaction to that, FDA did two important steps. The first was they did a label change. In the Warnings and Precautions section, they inserted a

comment about the safety signal with febrile seizures in the Southern Hemisphere. Secondly, FDA required a clinical trial to evaluate febrile seizures.

Shortly after that, the ACIP or the CDC's ACIP limited Afluria's use to children 9 years and older, which was the single most important public health intervention for this talk.

Subsequent to that, CSL requested a release from this required clinical trial, and FDA agreed to release CSL from that clinical trial several months later. And just about 2 months ago, FDA followed that with another label change and limited Afluria's use, approved use to children 5 years in age and older. So that's the timeline of events.

So you'll see here that, normally, we do a 1-year post-approval review, which would only take us through one and two influenza seasons. However, since the signal occurred really in the second season, you care about what happens in the third season to follow up to see if it actually happened -- what happened in Australia also happened in America. And so, we're going to do a special extended PAC review.

So this slide shows the trivalent influenza vaccine antigens in the Southern Hemisphere and the Northern Hemisphere by the influenza seasons. You'll notice that the Southern Hemisphere 2010 composition was identical to the 2010-2011, which is why it's important to do the extended PAC review.

Additionally, in order to understand what's going on, you also have to understand that it's not just the FDA labels for approved use that physicians are actually listening to. They're actually listening to what ACIP recommends for their use. And for Afluria, in 2009-2010, it was only recommended for 18 and above. And for the 2010-2011, it was initially recommended for 6 months and above and then was subsequently changed to 9 and above, as I said before, in reaction to the febrile seizure signal.

This slide shows the Afluria dose distribution in the United States. You'll notice that from August 2009 to June 2010, there were no pediatric doses. So no children should have been administered Afluria if they were between 6 months and less than 3 years. There was only distributed the 0.5 mL prefilled syringe, as well

as the multi-dose vials, totaling for about 7.8 million doses.

As I mentioned before, there were two major label changes that occurred during the PAC review period. The first was in July, where FDA notified physicians and healthcare providers about the Southern Hemisphere febrile seizure signal. And then, subsequent to that, in July of 2011, we changed the approved usage to 5 and above.

Additionally, CDC took the additional step of changing the vaccine information statement, and you can see here in the boxed area at the bottom of Section 5, it says very specifically, "One brand of inactivated flu vaccine called Afluria should not be given to children 8 years of age or younger, except in special circumstances." And it talks about those special circumstances.

So let's go to the review now. This table is the basic table where you show the serious deaths and nonserious reports among all age groups and among those 0 to 16 years of age, which is the purview of the PAC. You'll notice that there are no serious reports. All

pediatric reports are nonserious. And this is because, remember, that ACIP recommended use for only ages 18 and above.

More importantly, there were no febrile convulsions. But this was the season prior to the Southern Hemisphere season, and there are no safety signals identified upon close review.

All right. So we've done the first season. Now let's move to the season of interest in the Southern Hemisphere. There were two main issues going on in the Southern Hemisphere. First was fever. And this slide shows only about the fever.

There are three major studies that compared the CSL Southern Hemisphere vaccine, Fluvax, which is also identical to Afluria in the Northern Hemisphere, and compared to the other Southern Hemisphere vaccines in the same time period, given in the same population.

So in the uncontrolled cohort state in Western Australia among children less than 3, you'll see that the rate of fever was estimated to 40 to 50 per 1,000, compared to 5 for the rest of the vaccines. In a retrospective cohort study in New South Wales among

children less than 5, you see again a difference between 46 percent and 7 to 16 percent. And you see the similar pattern in New Zealand. In this case, it was only comparison to Fluvax and Vaxigrip. But nevertheless, you see the febrile reaction signal coming out.

This slide shows the febrile convulsions after CSL Fluvax. Passive surveillance estimated that the febrile convulsions occurred around 5 to 7 for 1,000, compared to 0.17 per 1,000 for Panvax, which is CSL's own monovalent vaccine, suggesting that it was not the 2008 H1N1 antigen that was at issue.

Similarly, you can see the uncontrolled cohort study here in Western Australia and then the cohort study, each basically saying that they're confirming in multiple different studies, confirming the same signal.

So after their investigation, what did the TGA conclude? Essentially, they concluded that no available clinical or epidemiologic factors offers a plausible explanation for the etiology of the observed events. CSL's vaccine, they noted, was administered in all cases where there was a known brand name, and there

are 21 different batches implicated, 2 batches of which accounted for more than 50 percent of the passively reported cases. So this is not active surveillance, but the passively reported cases.

The rapid onset was not consistent with an infectious etiology, with a mean of 7.2 hours, and respiratory symptoms were actually less common in post-vaccination cases, compared to those nonvaccine-related febrile seizures. Seventy-five percent of the cases were previously healthy, and there is no evidence of a priming effect.

So they went back to the clinical trial data and found that the baseline seropositivity to the H1N1 pandemic antigen was actually associated with lower rates of febrile responses. And in their laboratory investigation, they did find excess neuraminidase activity, but it's still, I would say, speculative as to that being the clear etiology.

So what did Australia do? Australia took two actions. Similar to the U.S., they took a regulatory action. In November of 2010, they limited the approved use to persons older than 5 years of age. They issued

a boxed warning, and they issued a public notification, basically saying that the audits of the CSL facilities to date show that there's no underlying cause for the adverse events identified, and the work continues.

Their ACIP, called the Australian Technical Advisory Group on Immunization, in March of 2010 limited use similar to our ACIP, and the exact wording is found below.

This is just a note about the FDA required clinical trial that I mentioned earlier. We originally required CSL to conduct a study in children 5 to 9 as a surrogate for moving into the age group of interest, which was really the less than 5-year-olds. It was a staged approach. We wanted to do that population first, the less vulnerable population first, and then move to the younger population.

FDA released CSL from this required clinical study under a good cause clause due to issues surrounding study feasibility and ethical concerns on whether you could really do a clinical trial when you know that there's a signal. So we released them from it.

So what's the current status then of CSL's

investigation? CSL is conducting in vitro and in vivo studies to evaluate cytokine and temperature responses to various formulations of the trivalent influenza vaccine, as well as the individual vaccine components.

Extensive investigations conducted to date have not identified root cause for the febrile events, and this is taken directly from their Web site.

All right. So let's move to the Northern Hemisphere vaccine to see did we see the same thing in America? Keep in mind that during this time, ACIP recommended only for ages 9 and above. So this was a very important public health intervention, which is probably why we aren't seeing -- we saw no febrile convulsions in this population.

And due to the small number of reports, again, we found no safety signals identified during the season. So the answer is, no, we did not see it. But it would probably be because of what ACIP did.

So, CSL, in light of all of this, in the following Southern Hemisphere vaccine which is ending just about now, committed to conducting two prospective observational cohort studies, one in Australia and one

in New Zealand. The Australian one is 600 children age 5 to 18 years, whereas, New Zealand, it's a smaller study, but equal, approximately equal power to assess and rule out the safety incidence rate that they found in the prior season.

All right. So what are our plans for vaccine safety monitoring in the U.S.? This is what you guys are going to vote on. So it's clear.

FDA and CDC will continue to conduct routine influenza vaccine surveillance. We will continue to do VAERS review where we will review serious adverse events, and we will continue to identify disproportional reporting through data mining.

In addition to that passive surveillance, we will also do active surveillance using CDC's Vaccine Safety Datalink, and we will partner with CDC to continue rapid cycle analyses for the high-priority adverse events of interest. So that's the plan.

In conclusion, there are no safety signals identified during routine surveillance of either Northern Hemisphere influenza season. FDA has revised the label to mitigate the risk of febrile reactions,

and more importantly, ACIP has not changed their recommendation for use. So it will continue to be only used in 9 and above.

The root cause investigation is ongoing, and CSL is conducting additional epidemiologic studies, which I talked about before, in the Southern Hemisphere, the results of which should be arriving shortly. And FDA recommends continued routine surveillance of Afluria.

Thanks.

DR. ROSENTHAL: Thank you for your very clear talk, Dr. Nguyen.

Dr. Rakowsky?

DR. RAKOWSKY: Yes, Dr. Nguyen, thank you for the nice talk.

Considering that the vaccinations in the Southern Hemisphere are probably going to be our springtime and there was a lot of noise in March of '10 that kind of led to the rapid movement done by the Australians and the New Zealand authorities, any noise this year?

I know the studies, you don't have the results from those yet. But any noise that you've been hearing about considering it's been 6 months since the flu

shots have been given down there?

DR. NGUYEN: The interim results of their passive surveillance has indicated that there hasn't been a problem. But again, that's because they've intervened already, and there is no immunizations being administered in children less than 9 there either.

So you're not going to really see febrile seizure concerns. Are we seeing elevated rates of fever? My understanding from their interim reports is that, no, we have not seen the subsequent elevated rates of fever. But again, that's following the interventions that I've already heard.

DR. ROSENTHAL: Dr. Romero?

DR. ROMERO: Let me speak into the microphone is what I better do. I have three questions, and you can answer them in any way you want.

So the first one is in regard to the noted neuraminidase, increased or excess neuraminidase activity. Did that vary between the two lots that represented 50 percent of the cases that had the seizures? What do you mean specifically by "neuraminidase activity?" So that's sort of one

question.

Second question, what data do we have regarding concomitant vaccine administration in these kids? In other words, were these children getting DaPT or some other vaccine along with them? Do we know anything about that?

And then, a question which maybe the people here can answer more than you. But will the PI, the product insert, reflect what is shown on slide number 11, which says that there was this one brand called Afluria should not be given to children 9 years of age and less, I believe it is. It's a little blurry for me to see.

So is that what's going to be included in our PI this year, and I'll stop with those questions now.

DR. NGUYEN: Great. So this is the slide 11, what you're referring to.

DR. ROMERO: Yes.

DR. NGUYEN: Because PIs don't usually talk about other vaccines, you'll see here this is the verbatim from the Warnings and Precautions section here. It's going to be different and that this is what's confusing

is that the FDA approved use is going to be different than the ACIP recommended use. And that right now is going to, as far as I know, going to stay the same.

And so, we can't -- we can't mirror what was already done in the vaccine information statement, which is really a recommended use and what's approved use based on data that the FDA has seen here. So that's the first question.

Let's talk about the vaccine, the concomitant vaccine administration here. I think this will help you.

So this is the TGA febrile seizures report, data lock point, May 7, 2010. There are 138 suspect reports. This is passive surveillance, remember. In children older than 5 years of age, there were 6 reports, very few, only 1 of which was actually confirmed as a febrile seizure.

In contrast, there was 132 reports less than 5 years of age, 95 of which were confirmed. And CSL's vaccine, as you can see here, was administered exclusively among the majority of them, whereas the other ones had concomitant vaccination. So that

answers some of your question. I can't get more specific than that.

The neuraminidase activity. So this is tricky because this is done by the TGA. I have what's only available publicly, and I can only talk about what's available publicly. And they did not describe in detail what their methods they used, the assay they used.

And I guess I can refer you back to the actual document published October 8th, and they do give a little bit more information. And I can get that to you after the talk.

DR. ROMERO: Thank you.

DR. ROSENTHAL: Yes. Dr. Balis?

DR. BALIS: Just a quick question. The New Zealand study, is there a younger age limit in those patients? It just says less than 18.

DR. NGUYEN: There is none.

DR. BALIS: So they went down below the age of 5?

DR. NGUYEN: No. New Zealand kept their recommendation as well, and it's 5 -- well, the study will capture any vaccination that's observed. New

Zealand has recommended use 5 and above, just like everyone else.

DR. ROSENTHAL: Yes. Dr. McMahon?

DR. MCMAHON: Hi. That was a great talk. I had a couple of just questions, not having been familiar with this information.

Is the vaccine, the Australian vaccine exactly the same as the United States vaccine? Or does it have different adjuvants or is there anything different about it?

DR. NGUYEN: It is antigenically identical to the U.S. vaccine. There is a minor strain difference, but antigenically they are equivalent. The seed in one of them, I believe, is a little bit different, but it still generates the same immune response and has the same specificity to them. But other than that, it is considered antigenically equivalent.

And the rest of the vaccine, as far as I know -- and I don't know if CSL is actually here, but as far as I know, they are identical. And it sounds like OVR would like to make a comment.

DR. FINN: I'm Theresa Finn from the Office of

Vaccines.

I think we should make an important point is that although Michael is absolutely correct that they are often identical vaccines, however, we should bear in mind that the recommendations for the strains to be included in the Southern Hemisphere may not be the same as the recommendations for the strains to be included in the Northern Hemisphere. This is all just -- that's all based on surveillance and WHO and FDA input and CDC input.

So there are years when those strains will be the same and the vaccine will be the same, but FDA does not approve the Southern Hemisphere version of the vaccine.

DR. ROSENTHAL: Will you repeat your name for me? I'm sorry.

DR. FINN: Theresa Finn.

DR. ROSENTHAL: Thank you.

Dr. McMahon?

DR. MCMAHON: Sorry. That was one of part. And then the other question I had is the age cutoff at 9. I mean, I can see here that younger is higher risk, blah, blah. But I can't tell the 9, where that came

from.

DR. NGUYEN: So there's a couple of things. There are two main reasons why this is there. Let me pull up the slide to help out here.

DR. ROSENTHAL: I thought it was 8.

DR. MCMAHON: Less than 9 or --

DR. NGUYEN: Okay. So the first reason --

MALE SPEAKER: It's through age 8.

DR. MCMAHON: Less than 9.

DR. NGUYEN: So the first reason is during the ACIP Working Group meeting, the ACIP Working Group decides on what they are allowed to vote on. And so -- the greater ACIP group, and so when they put this up, they discussed about what age cutoff to use.

And you can see here, this is clinical trial data where you can see the differences between Afluria and its active comparator, and this is just the rates of fever. And you can see that it sort of diminishes at 5 to 9, at 16 to 9 percent.

Additionally, there's a programmatic issue here in the sense that you want to reduce the amount of -- if there's a fever reaction concern, you want to reduce

the amount of exposure to children. And in children 8 years and under, they recommended if it's the first year, they get two vaccines, not just one. And so, there's a programmatic reason and there's sort of a clinical trial data reason, and that's why -- that's where it's coming from.

And similarly, in Australia, it's 10, not 9. But again, it's programmatic reasons there. For 9 and under, I believe, they get two vaccines. Instead of for us, it's just 8 and under.

DR. MCMAHON: Okay.

DR. NGUYEN: But it's reducing the risk to children.

DR. MCMAHON: Okay. That's interesting. So the other thing is, is the adverse event fever, seizure --

DR. NGUYEN: In this slide, it is.

DR. MCMAHON: -- or seizure and fever?

DR. NGUYEN: Well, there's two. There is fever, as well as febrile convulsions. This slide shows fever. I also showed -- there are two separate slides for rates of fever and another slide for rates of febrile convulsions.

DR. MCMAHON: But I was just wondering whether it's really what's going on here is that the kids are getting fever, and then if they're in a susceptible age range, they get the febrile seizure. Or whether given fever, is the risk of seizure increased even given fever with this vaccine? Do you see what I mean?

DR. NGUYEN: Could you repeat your question?

DR. MCMAHON: Well, what I mean is so one possibility is that it's the fever itself, period. The fever is more likely with this vaccine in a certain age range. Another possibility is that the risk of seizure goes up even with given the risk of fever? Is that true, too?

DR. NGUYEN: I see what you're saying. I'm not sure we have the data to be able to differentiate that fact. I think it's a good point. I don't think unless -- I know that there are trained neurologists here, if they want to comment? Dr. Mink or any others?

DR. ROSENTHAL: Dr. White, you had a question?

DR. WHITE: Yes. I think doesn't the incidence of febrile seizures in all populations go down well before 5 years of age? So, I mean, when we're talking about

stratifying this risk group, the likelihood of a febrile seizure in a child over 5 is much lower than younger children even with the same fever, same rate of rise. Is that correct?

Thank you.

DR. ROSENTHAL: Dr. Nguyen, can you take us back to the voting slide? Are there other questions while we're getting back to that point?

(No response.)

DR. ROSENTHAL: All right. No, this was the one that told us exactly what the agency was going to do, which I found very helpful, by the way. So thank you for including that slide.

And then the next one, which actually articulates the question. So there is a recommendation from the agency that continued routine surveillance of Afluria will continue, and does the Advisory Committee concur with that recommendation?

All in favor, please raise your hands.

(Show of hands.)

DR. ROSENTHAL: Any opposed?

(No response.)

DR. ROSENTHAL: And any abstentions?

(No response.)

DR. ROSENTHAL: No abstentions, no opposition.

Okay. Dr. Vaida, will you get us started going around the table?

DR. VAIDA: Allen Vaida. I voted yes.

MS. CELENTO: Amy Celento. Yes.

MS. EICHNER: Marilyn Eichner. I voted yes.

DR. BALIS: Frank Balis. I voted yes.

DR. REED: Michael Reed. I voted yes.

DR. CHAPPELL: Rick Chappell. Yes.

DR. ROMERO: Jose Romero. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. MINK: John Mink. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. DURE: Leon Dure. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. BRINKER: Jeff Brinker. Yes.

DR. WHITE: Michael White. Yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. KOCIS: Keith Kocis. Yes.

DR. ROSENTHAL: Okay. Thank you very much.

So now we're ready to move on to Fluarix, and Dr. Melisse Baylor will give the first presentation. And just once again, I'll just note that Dr. D'Angio remains recused from this discussion and from the vote as well.

DR. BAYLOR: The good news is that it's 5:30 p.m., and the presentation is fairly straightforward. Okay.

The good news is this presentation is fairly straightforward, and it's the last vaccine. So that's the good news.

But my name is Melisse Baylor, and I'm a medical officer in the Division of Vaccines and Related Product Applications. I'll be presenting the pre-licensure safety information for Fluarix influenza vaccine.

Fluarix is a trivalent inactivated seasonal influenza vaccine that's indicated for the active immunization of disease due to the influenza subtypes that are contained in the vaccine. Each vaccine dose is 0.5 milliliters and contains 15 micrograms of hemagglutinin from 2 influenza A subtypes, H1 and H3, and 1 influenza B type.

Fluarix is supplied as a single-dose prefilled

syringe without preservative.

Fluarix was first licensed in the United States in August of 2005 for use in individuals 18 years of age and older. Fluarix was the first influenza vaccine that was approved under the accelerated approval regulations, and these regulations were used because of the 2004-2005 influenza vaccine shortage.

Fluarix was subsequently granted traditional approval in adults in October of 2009. So while accelerated approval was based on studies using antibody response as a surrogate marker, traditional approval was based on the results of a clinical endpoint study. The recommended use of Fluarix was expanded to children 3 years of age and older in October of 2009.

The safety database pre-licensure that supported the subsequent licensure of Fluarix was made up of three studies -- one main or primary study and two supportive studies. The primary study, Study 005, was a Phase III randomized, observer-blind study in healthy children from 6 months to less than 18 years of age. Study subjects were randomized to receive either

Fluarix or a different U.S.-licensed influenza vaccine.

A total of 2,115 children received Fluarix. As shown here, this included 375 children from 6 months to less than 3 years of age, and the majority of subjects, as you can see, were 3 to less than 18 years of age.

The two supportive studies were Study 056 and Study 062. One hundred fifty-seven children from 6 months to less than 6 years were enrolled in 056. The study population was older in Study 062, which enrolled 224 subjects from 6 to 13 years of age.

And I have to point out here that Fluarix was approved in children 3 years of age and older only because of lower antibody response in children younger than 3 years. The licensure in this age group was not related to safety concerns in children younger than 3 years of age.

The dosing and dosing schedules were the same in all three studies, and they're all consistent with the ACIP recommendations that were current at the time that the studies were initiated. The vaccine dose varied with age. Subjects younger than 3 years of age got a 0.25 mL dose, and older children received a 0.5 mL

dose.

The number of doses received varied by age and by vaccine history. So subjects who were younger than 9 years of age and had never received an influenza vaccination received 2 doses of study vaccine administered 4 weeks apart. Subjects who were younger than 9 years of age and had previously received an influenza vaccination received 1 dose during the study, and all subjects who were 9 years of age and older, regardless of their vaccination history, received 1 dose.

This slide points out the major differences in the primary and the two supportive studies. The primary study enrolled subjects from 6 months to less than 18 years of age, while the supportive studies enrolled subjects from 6 months to 13 years.

The age subgroups differed in the three studies, and I just wanted to point out that the second age group that you see in the slide is less than 5 years in the primary study and 3 to less than 6 years in the supportive studies. And the primary study enrolled both vaccine naive and vaccine experienced patients,

while the supportive studies enrolled only vaccine naive subjects.

Safety follow-up for the primary study was 180 days after the first vaccination. In one supportive study, subjects were followed for 30 days after the first dose of vaccine, and in the other, they were followed for 7 months after the first dose of vaccine.

The primary study was conducted under U.S. IND, but the supportive studies were not. So these studies were both conducted in Europe, and the study protocols for those studies were not reviewed by FDA.

Of note, the primary study had a U.S.-licensed comparator while the supportive studies did not. And because of the differences in these studies, the safety results of the primary study and the two supportive studies will be presented separately.

In the primary study, parents or legal guardians were queried about specific adverse reactions both at the injection site and systemic adverse events on the day of vaccination and for the subsequent 3 days. Unsolicited or spontaneously reported AEs were monitored for 21 days post-vaccination, and serious AEs

were followed for the entire study period of 180 days.

In this study, subjects were seen in clinic 4 weeks after the last dose as a safety follow-up and were contacted by telephone 6 months after the first dose to collect safety information.

There were no deaths in the primary study, and overall serious adverse events were reported in the same percentage of subjects in both vaccine arms. But when you look at the lower part of the slide at the percentage of serious adverse events by age subgroup, the percentage of subjects with serious AEs was similar by treatment arm in the three age subgroups.

But the percentage of subjects with serious AEs was higher in the 6 to 35 month subgroup. So you see it's similar between Fluarix and the active control for each age subgroup, but it is highest overall for both Fluarix and the control in the 6 to 35 month.

And just again to remind you that Fluarix isn't licensed in this first age subgroup, but it's not because of safety concerns. It's due to lower antibody response.

And this slide lists the serious AEs that occurred

during the 4 weeks after vaccination. In this time period, there were 5 subjects with SAEs in the Fluarix arm and 3 in the active control arm, which is approximately 0.2 percent in each arm.

The individual serious adverse events were appendicitis in a 14-year-old female on day 10, fecal impaction in a 7-year-old male on day 9, and then a febrile seizure was reported on day 4 in a 13-month-old male. He was vaccinated on January 24th. Two days later, he had a temperature of 38.3 degrees and was given acetaminophen. Two days after that, on day 4 post-vaccination, he had 2 minutes of staring left with an arched back and appearing frozen.

He was taken to the emergency room where at the time he arrived, he was alert and active. He was discharged with no lab work, no EEG, and he was seen by his pediatrician the next day. He was again alert and active. No further workup was done. But in the investigator's judgment, the relationship to the study vaccine could not be ruled out.

Then to go on, we have a 6-month-old male who was diagnosed with RSV bronchiolitis and pneumonia on day

27, an 11-month-old female with asthma was diagnosed with an exacerbation of her asthma and pneumonia on day 5.

And in the control arm, we had two subjects with pneumonia, a 2-year-old male who was diagnosed or symptom onset, I'm sorry, at day 10, and a 3-year-old male with symptom onset at day 9.

A 2-year-old male had gastroenteritis several weeks after the last dose of study vaccine also in the active control group. And the SAE due to a febrile seizure was the only serious adverse event judged as possibly related to a study vaccine.

The most frequently reported solicited adverse reaction was injection site reactions. Of these, pain at the injection site was reported in 53 percent of subjects and redness at the injection site in 21 percent. Of solicited systemic adverse events, the most common adverse events varied by age, but they were similar in the two treatment arms.

So in the youngest children, you saw irritability, drowsiness, and loss of appetite. In the 3- to 5-year-olds, there was just irritability. And over 5, fatigue

and muscle ache.

And because of the previous presentation, the incidence of fever is presented here also. And fever was measured orally, and fever was defined -- temperature was measured orally, and fever was defined as a temperature of 38.8 degrees or higher. And these are percentages for subjects who had fever on the day of vaccination or the subsequent 3 days.

As you can see, the incidence of fever is highest in the youngest age group, the 6 to 35 months, and the rate of fever decreased with increasing age. But overall, the percentage of children with fever was similar between the two vaccine arms.

Now to switch to the two supportive studies, in these studies, solicited local and systemic adverse events were collected in the same way as in the primary study. Information on unsolicited or nonserious adverse events was collected for 30 days in both of these studies, and serious adverse events were followed for the entire study period in both of these studies. But the entire study period was 30 days in one of them and 7 months in another.

And in both trials, there were visits to the study sites at 4 weeks after the last dose, and in the other -- in the one study, there was a subsequent phone call at 7 months for collection of safety information.

In the two supportive studies, a total of 376 children from 6 months to 13 years of age were enrolled and vaccinated. There were no deaths in either study. Serious adverse events reported during the entire study period were reported in 6 subjects, or 1.6 percent of subjects, and these included what's shown on the slide -- brain trauma, gastroenteritis, constipation, enteritis, hematuria, and tonsillitis.

Of these, only the gastroenteritis and the constipation were reported within 2 weeks of vaccination, and none of these SAEs were judged by the investigator as being related to study vaccine.

So the most common nonserious solicited adverse events in these two supportive studies were also adverse reactions at the injection site -- pain, redness, and swelling. The ranges are used here because these adverse events were reported by study and by age subgroup, and so there's no total data pooling

of the studies.

So, as you can see, there is a wide range for pain. It was the highest in the age subgroup 10 to 13 years and lowest in the youngest age group of 6 to 35 months.

Solicited systemic AEs reported in at least 20 percent of subjects varied by age subgroup, and they were drowsiness, irritability, and loss of appetite in the youngest age group; drowsiness in 3 to less than 6 years; and in the older children, 6 to 13, it was headache, fatigue, and myalgia.

Again, the fever is shown in the bottom of the slide, and it's presented again by age subgroup. Fever was reported for 33 percent of subjects 6 months to less than 36 months of age, 22 percent of subjects 3 to less than 6 years of age, and 5 percent from 6 to 13 years of age.

Of note, the definition of what was fever and the route of measurement varied. In the youngest age group, parents and legal guardians were instructed to take the temperature rectally. And in the other two groups, they were to take axillary temperatures. Fever

was defined as a temperature of 38 degrees or higher in the youngest age group and as a temperature of 37.5 degrees or higher in the older two age groups.

So, in conclusion, there were no deaths in the three pre-licensure pediatric studies of Fluarix. There was one SAE that was judged as vaccine related by the investigator, and that was a febrile seizure in a 13-month-old.

Since this was the only febrile seizure in the three studies, that results in one seizure in 2,015 children studied, or less than 0.1 percent of subjects. If you narrow it down to subjects who were less than 36 months of age, it's one seizure for 428 subjects, or 0.2 percent.

The percentage of subjects with fever varied by age. In the age subgroup 6 months to less than 3 years, the percentage of children with a fever within 4 days of vaccination was 16.4 percent in the study where temperature was measured orally, and it was 33.3 percent in the study in which temperature was measured rectally.

In children from 3 years to less than 5 years in

one study and 3 years to less than 6 years in the other, temperature was measured by axillary route, and fever was reported in 8 percent in one study and 21.7 percent in the other study. But overall, there were no clear safety signals were identified in the pre-licensure studies.

DR. ROSENTHAL: A few questions. Dr. Wagener and then Dr. Romero.

DR. WAGENER: Very briefly, in the supportive studies, did they separate any of the fever data based on whether this was a booster shot versus whether it was a primary? Similar to the other vaccine.

DR. BAYLOR: The first dose or the second dose? Because they all were naive. So they both had two doses, and fever was generally higher after the first dose. The figure you had was fever after any dose. So --

DR. ROMERO: Concerning the fever, was there any difference in the maximum intensity of the fever? In other words, were there more children that had higher fever in one group than another?

DR. BAYLOR: In the number with Grade 3 fevers or

whatever?

DR. ROMERO: Yes. Yes.

DR. BAYLOR: No. The severity was not different.

DR. ROSENTHAL: Other questions?

(No response.)

DR. ROSENTHAL: All right. Let's move along with our next and final presentation by Dr. Patricia Rohan.

DR. ROHAN: Sorry. Just a moment.

(Pause.)

DR. MURPHY: Patricia, will you just say a sentence about your background, too? Thank you.

DR. ROHAN: Good afternoon, late afternoon. I'm Patricia Rohan, a medical officer in the Office of Biostatistics and Epidemiology. And I will be reviewing the pediatric safety and utilization for Fluarix.

I can quickly go over some of the introductory slides. They've been covered by my colleague, Dr. Baylor. But I did want to point out that Fluarix was originally approved in adults, and later, expanded age usage was approved on the 19th of October 2009. So that's well into a particular seasonal flu cycle, and

that becomes important when you're looking at the data.

The current U.S. pharmacovigilance plan includes routine pharmacovigilance. There have been no planned, ongoing, or completed targeted safety studies. In addition, the sponsor has included several voluntary elements. They provide expedited reporting and conduct annual analyses for each of the following events of interest -- Guillain-Barre syndrome, multiple sclerosis, and optic neuritis.

And these events were chosen based on the IOM Immunization Safety Review Committee report of 2004, which cites available evidence as inadequate to accept or reject the causal relationship with influenza vaccine.

There has been a single safety-related labeling change since U.S. licensure. The Warnings and Precautions section has had a statement added. "The tip caps of the prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals."

And please note that this above label change, which was implemented in 2010, was not prompted by any

adverse events related to latex allergic reactions after Fluarix.

U.S. distributed doses from October 19, 2009, through October 18, 2010, include a total of 6,481,089 net doses of Fluarix distributed within the U.S. There are no data available regarding Fluarix age-specific use in the U.S.

Fluarix was first recommended for use in children by the CDC Advisory Committee on Immunization Practices, or ACIP, in August 2010. This is also 10 months after FDA approval of expanded age usage in children 3 years of age and older. That is, it was basically for the subsequent flu season of 2010-2011.

And this is a tabular summary of available influenza products in the U.S. And as you can see for the 2009-2010 season, ACIP recommended Fluarix for use in adults, and it was only the following season where children were recommended.

This is a summary of the adverse events reported to VAERS for the year following expanded age usage. In the 3 to 16 year age group, there were a total of 6 adverse events -- 2 serious events, which were non-

U.S., and 4 U.S. reports, all nonserious. In addition, I have included information that we have about children younger than the approved age usage range, and you can see that there were three. They were serious, and they were non-U.S.

The serious reports, the five that were summarized in the preceding table, were reported with no concomitant vaccines. The age range was 9 months to 6 years, with a median age of 2 years. There were no deaths. All five children were hospitalized, and they were all non-U.S.

This is a brief summary of the available information that we have on those reports. A 9-month-old with upper abdominal pain, cholecystitis, pyrexia. This child had a history significant for prematurity, enterocolitis, and small intestine volvulus.

A 1-year-old male with balance disorder and an abnormal neurological examination; a 2-year-old female with febrile convulsion; a 4-year-old female with febrile convulsion; and a 6-year-old male, body temperature normal, injection site erythema and swelling, and an abnormal neurological exam.

This is a summary of the U.S. VAERS reports in 0 to 16-year-olds for the year following expanded age usage approval. For four children, three had reported concomitant vaccines. The age range was 6 to 14 years of age, with a median age of 9 years. There were no deaths, no serious adverse events.

This is a summary of those four U.S. reports. A 6-year-old female with erythema and local swelling; a 6-year-old male with cough, fatigue, malaise, and pyrexia; a 12-year-old female with injection site erythema and swelling; and a 14-year-old male feeling cold, hypoaesthesia, paraesthesia.

We additionally looked at febrile convulsion, and I think it goes without saying from the preceding presentations why we did that. And I footnoted based on the Australian and New Zealand experience with the 2010 Southern Hemisphere formulation of a particular influenza virus vaccine.

So we looked at febrile convulsions following use of Fluarix, and as you can see, there were no U.S. reports. There were a total of 3 non-U.S. reports, 2 in children less than 3, and 1 in a child in the 3 to

16 year age range.

Subsequently, we also looked at febrile convulsions for individuals 3 years of age and above, in addition to the 4 individuals who I have just summarized. All the reports of the four are non-U.S. The 2-year-old female, there's a 13-year-old male with vomiting and diarrhea, and a 4-year-old female and a 2-year-old male with acute upper respiratory infection, all of whom were hospitalized.

So this is additional data that we carried forward to look through July 15th of this year, not just the 1 year following licensure.

This completes the pediatric safety review for Fluarix in 3- to 16-year-olds. No new safety concerns have been identified, and no additional studies have been required to assess known safety risks, to assess signals of serious risks, or to identify unexpected serious risks.

FDA, therefore, recommends continued routine monitoring for new safety signals. We ask the committee do they concur?

Thank you.

DR. ROSENTHAL: Thank you very much.

Any questions for either Drs. Rohan or Baylor?

Yes, Dr. Balis?

DR. BALIS: Were these serious adverse events all attributed to the vaccine?

DR. ROHAN: I'd have to go back and look. Sometimes they checked that they thought that it was, but they don't necessarily in post-marketing reporting always give us that information.

And actually, we encourage people to not make a decision whether they think it's related if an adverse event occurs. We would much rather have them report it to us, not screen it for that judgment, and then look at the trends or patterns. Then we get much more information that way.

But, so some of them were. Some weren't. But not in any -- there are so few reports that there wasn't any pattern.

DR. ROSENTHAL: Other questions?

Oh, yes. Okay. Dr. Vaida? Thank you.

DR. VAIDA: Just a simple question, and maybe this was gone through before. With the age breakdowns, like

on slide 7, I'm talking about the age groups, like what the Novartis is greater than 4 and this was now you're looking at greater than 3. Where did those cutoffs come from?

I know what the greater than 9 on the other one, but I mean, it is very confusing for the practitioners. We get reports in through our system because a lot of states will do that, and they gave it to a 3-year-old, a 4-year-old.

DR. ROHAN: I think Dr. Finn is going to provide response.

DR. FINN: Okay. What we have on the slide here are the recommendations for the ACIP. And in some cases, these reflect the age, and for most of them, in fact, these reflect the approved ages for which these products can be -- approved age groups to which these products can be administered.

So, for example, if we look at Fluvirin, which is the one that you pointed out, it is approved for use in children 4 years of age and older, okay? And I am -- that was approved before my time, but I understand it's on the basis of immunogenicity data.

Fluzone is approved for use in children 6 months of age and up, and that's also based on data. FluMist is approved for use in children 2 through 49 years of age. That's based on data.

All of these, the FDA approvals are based on data. ACIP recommendations may be based on other things, and we heard some of that in the last presentation. For example, they take into consideration programmatic issues.

DR. VAIDA: So it's based on data that was supplied to you, compared to what you were --

DR. FINN: And is in the package insert.

DR. VAIDA: -- like rather than ask tested above 2 or something to try to get a little standardization? It was just what they supplied to you?

DR. FINN: Yes. And so, what you heard for when Dr. Baylor gave her presentation, she said that the company, the manufacturer had conducted studies in children 6 months of age and up.

However, FDA reviewed those studies, and based on the immunogenicity of that particular product, it gave use of that product, approved use of that product 3

years of age and up. Okay?

DR. ROSENTHAL: Other questions? Any other discussion?

Can we go back to the voting slide, please?

All right. Well, after these two presentations on Fluarix, does the committee concur with the agency that it makes sense to return to routine monitoring for new safety signals with this vaccine?

All in favor, all supporting that?

(Show of hands.)

DR. ROSENTHAL: Okay. Great. Any opposition?

(No response.)

DR. ROSENTHAL: Any abstentions?

(No response.)

DR. ROSENTHAL: So it's a unanimous yes.

All right. Let's go around for a vote. Dr. Kocis?

DR. KOCIS: Keith Kocis. Yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. WHITE: Michael White. Yes.

DR. BRINKER: Jeff Brinker. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. DURE: Leon Dure. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. MINK: John Mink. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. ROMERO: Jose Romero. Yes.

DR. CHAPPELL: Rick Chappell. Yes.

DR. REED: Michael Reed. Yes.

DR. BALIS: Frank Balis. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

MS. CELENTO: Amy Celento. Yes.

DR. VAIDA: Allen Vaida. Yes.

DR. ROSENTHAL: Excellent. Thank you very much.

So, just a few housekeeping points. Tomorrow morning, we start at 8:00 a.m. We start in this room. So come and be fresh. I hope everyone gets a good night's sleep.

The next point --

DR. MURPHY: You should have your slides for tomorrow. Did they give those -- they handed them out? Just want to make sure everybody got the slides for tomorrow.

DR. ROSENTHAL: Yes. Yes, I think so. So that's

good. So we've got that.

Also, please bring back the confidential CD so that it can be turned in tomorrow at the conclusion of the meeting tomorrow. Actually, we've got some very exciting things to discuss tomorrow. So this is -- we'll have a good meeting.

And then, finally, if people can just follow through on Dr. Ellenberg's recommendation regarding reading through this ethics material, sign the form saying that you've reviewed it, and please return that to him so we can check that box.

Are there any other housekeeping things, Dr. Murphy?

I'd like to remind everyone again to please refrain from any discussion regarding the content of the meeting outside of the meeting room. The agency really wants to benefit from all discussions and be able to access all discussions by having them on the record. So let's try and maintain our standards of transparency and openness and refrain from any discussions of content outside of this meeting.

And if anyone has any process comments that they'd

like to send my way, that's always okay.

DR. MURPHY: Yes, really, I think we'll probably try to have a handout for you tomorrow. I'm not sure where we'll Xerox it, but we'll try to get one for you tomorrow that you can look at. So that we get to the afternoon presentation, you can comment on that and have it in hand.

DR. ROSENTHAL: All right. We're adjourned.

Thank you very much.

DR. MURPHY: Yes. Thank you guys very much.

(Whereupon, at 5:55 p.m., the meeting was concluded.)